Remarks

The Office Action mailed April 8, 2003 has been received and reviewed. Claims 48-53 having been cancelled, the pending claims are claims 21-26, 29-47, 54, and 55. Reconsideration and withdrawal of the rejections are respectfully requested.

Allowed Claims

Applicants thank the Examiner for indicating that claims 21-26, 29-33, and 36-47 are allowable.

Information Disclosure Statement

A copy of the PTO-1449 mailed March 20, 2001, considered and initialed by the Examiner was received with the previous Office Action mailed September 26, 2002. The Ling et al. citation, "Synthesis of Antigenic Determinant Tyr-CGRP=(27-37) of Calcitonin Gene-Related Peptide," *Chemical Abstracts, 122*(15):1117, Abstract No. 122:188122f (1995), was lined through on the PTO-1449 and was not considered by the Examiner. The Examiner provided no explanation for lining through this citation.

With the previous Amendment and Response mailed December 26, 2002, Applicants provided Exhibit A, which included a copy of page 3 of the PTO-1449 (mailed on March 20, 2001) and a copy of the Ling et al. abstract. Applicants requested in that Examiner consider Ling et al., "Synthesis of Antigenic Determinant Tyr-CGRP=(27-37) of Calcitonin Gene-Related Peptide," *Chemical Abstracts, 122*(15):1117, Abstract No. 122:188122f (1995), the Ling et al. Or, if the Examiner was unable to consider the Ling et al. abstract, Applicants requested that the Examiner provide an explanation of why he was unable to do so.

Applicants respectfully repeat their request that the Examiner consider the Ling et al., abstract and so indicate on the PTO-1449. Or, if the Examiner cannot consider this reference, he is respectfully requested to explain why he is unable to do so. To assist the

Examiner, as a courtesy, copies of page 3 of the PTO-1449 (previously mailed on March 20, 2001, citing Ling et al.) and the Ling et al. abstract are provided herewith, as Exhibit A.

Election of Species

With the indication of the allowance of generic claims 21-26, 29-30, 32, 33, and 36-47, Applicants respectfully request the rejoinder and examination of non-elected species SEQ ID NO:1 and SEQ ID NO:6-23. Thus, Applicants request the rejoinder and examination of species SEQ ID NO:1 in claim 31 and the rejoinder and examination of withdrawn claims 34 and 35, drawn to species SEQ ID NO:6-23.

In a response to the Restriction Requirement of May 2, 2002, Applicants elected, with traverse, Group I, claims 21-26 and 29-47, drawn to methods of inhibiting CGRP binding to one or more CGRP receptors. The Restriction Requirement included an Election of Species; with the election of Group I, Applicant was further required under 35 U.S.C. 121 to elect a species from one polypeptide from SEQ ID NO:1, 2, and 6-23. In a Supplemental Response to Restriction Requirement (submitted July 2, 2003), Applicants elected the species SEQ ID NO:2. This election was made with traverse to the extent that it is understood that (a) the requirement will be withdrawn upon the finding of an allowable genus; and (b) any species withdrawn from consideration will be transferred to the elected subject matter unless it is found patentably distinct from the elected or allowed claims.

In the Office Action mailed September 26, 2002, the Examiner acknowledged the Applicants' species election, of SEQ ID NO:2. The Examiner also acknowledged the Applicants' traversal, stating "the traversal is made to the extent that the requirement will be withdrawn upon the finding of an allowable genus, and any species withdrawn from consideration will be transferred to the elected subject matter unless it is found patentably distinct from the elected or allowed claims" (see page 2, Office Action mailed September 26, 2002). The Examiner concluded with the statement, "[a]s no generic claim has been indicated to be allowable, this

request will be held in abeyance until such time" (see page 2, Office Action mailed September 26, 2002).

Applicants respectfully submit that claims 21-26, 29, 30, 32, 33, and 36-47 are generic to species SEQ ID NO:1, 2, and 6-23. Thus, with the Examiner's indication of the allowability of generic claims 21-26, 29, 30, 32, 33, and 36-47, Applicants respectfully request the rejoinder and examination of non-elected species SEQ ID NO:1 and 6-23. Applicants request the rejoinder and examination of species SEQ ID NO:1 in claim 31 and the rejoinder and examination of withdrawn claim 34 (drawn to species SEQ ID NO:6-17 and SEQ ID NO:23) and withdrawn claim 35 (drawn to species SEQ ID NO:18-22).

The 35 U.S.C. §112, First Paragraph, Rejection

The Examiner rejected claims 54 and 55 under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Applicants respectfully traverse this rejection.

Specifically, the Examiner continues to assert that a peptide that is an antagonist of CGRP cannot be vasoactive. To support this conclusion, the Examiner cites the definition of antagonist from Dorland's Illustrated Medical Dictionary; that an antagonist is "a substance that tends to nullify the action of another, as a drug that binds to a cell receptor *without eliciting a biological response*" (see pages 2-3 of the Office action mailed April 8, 2003).

Applicants respectfully submit that the Examiner's interpretation and application of this definition is inappropriately restrictive. And, Applicants respectfully submit that the Examiner's absolute conclusion from this definition, that a CGRP antagonist cannot elicit a biological response and thus cannot be vasoactive, is incorrect.

Stedman's Medical Dictionary (Exhibit B) defines an antagonist as "[s]omething opposing or restricting the action of another; certain structures, agents, diseases, or physiologic processes that tend to neutralize or impede the action or effect of others." Merriam-Webster's

Collegiate Dictionary (Exhibit C) defines an antagonist as "an agent of physiological antagonism: as . . . a chemical that acts within the body to reduce the physiological activity of another chemical substances (as an opiate); especially one that opposes the action on the nervous system of a drug or substance occurring naturally in the body by combining with and blocking its nervous receptor." And, the online Merck Manual of Diagnosis and Therapy (Exhibit D) states "[a]ntagonists interact selectively with receptors but do not lead to an observed effect; they reduce the action of another substance (agonist) at the receptor site involved." Applicants submit that an antagonist, by blocking the binding of an agonist to its receptor, can:

(1) nullify the action of the agonist (see Dorland's Illustrated Medical Dictionary);

(2) oppose or restrict the action of the agonist, tending to neutralize or impede the action or effect of the agonist (see Stedman's Medical Dictionary);

(3) can act within the body to reduce the physiological activity of an agonist (see Merriam-Webster's Collegiate Dictionary); or

(4) reduce the physiological activity of the agonist (see Merck Manual of Diagnosis and Therapy).

Thus, an antagonist will often have a biological or physiological effect. There is nothing in these various definitions that precludes a CGRP antagonist from exhibiting a vasoactive effect.

Further, Applicants submit that the vasoactive effect of various known CGRP antagonists is well documented in the scientific literature. For example, Gardiner et al. (Gardiner et al., "Antagonistic effect of human alpha-CGRP [8-37] on the *in vivo* regional haemodynamic actions of human alpha-CGRP," *Biochem. Biophys. Res. Commun.* 1990, 171, 938-943, a copy of which is enclosed herewith as Exhibit E) demonstrates that human alpha-CGRP [8-37] (1) "is an effective antagonist of the cardiovascular actions of human alpha-CGRP *in vivo*" and (2) causes "an increase in mean arterial blood pressure, together with renal, mesenteric and hindquarters vasoconstrictions" when administered to rats at a dose of 300 nmol/kg/min (Gardiner et al., see abstract). Thus, human alpha-CGRP [8-37] is both an antagonist and vasoactive. And, as another example of the *in vivo* vasoactive effects of CGRP

antagonists, the Examiner is directed to U.S. Pat. No. 6,521,609 (the '609 patent, a copy of which is enclosed herewith as Exhibit F). The '609 patent teaches the administration of various CGRP antagonists for the treatment of menopausal hot flashes caused by vasodilation and increased blood flow, demonstrating the *in vivo* vasoactive effect of CGRP antagonists ('609 patent, see abstract). Thus, Applicants submit that it is well accepted that being a CGRP antagonist and having a vasoactive effect need not be mutually exclusive activities.

The Examiner also asserted that the specification provides no instruction or guidance of how to make a CGRP antagonist that is vasoactive and provides no working examples of such vasoactive peptides (page 4, Office Action mailed April 8, 2003). Applicants respectfully disagree and direct the Examiner's attention to, for example, page 17, lines 17-28, Example 2, and Example 3 of the specification. Page 17, lines 17-28, of the specification provides general instruction and guidance for the *in vivo* testing of CGRP antagonists for the vasoactive effect of reversing the hypotension and tachycardia induced by the administration of LPS. Example 3 of the specification provides instructions and guidance for the *in vivo* testing of the CGRP antagonists of the present invention for the vasoactive effect of inhibiting the hypotensive effect of CGRP. And, Example 2 and Figure 2 provide a working example demonstrating the vasoactive effect, the inhibition of h–α-CGRP-induced relaxation of isolated pig coronary, of CGRP antagonist of the present invention. Applicants submit that the specification provides adequate instruction and guidance to make and use the claimed vasoactive, antagonistic peptides.

In view of the discussion above, Applicants respectfully request the reconsideration and withdrawal of the rejection of claims 54 and 55 under 35 U.S.C. §112, first paragraph.

The 35 U.S.C. §112, Second Paragraph, Rejection

The Examiner rejected claims 54 and 55 under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. Applicants respectfully traverse this rejection

The Examiner asserted that the metes and bounds of the recitation "vasoactive" claim 54 can not be determined. Applicants respectfully disagree and submit that the specification provides adequate guidance for determining the metes and bounds of the claimed vasoactive peptides. As defined in the specification (p. 11, lines 1-4), the "term 'vasoactive peptide' as used herein refers to peptides with physiological activity, particularly, but not necessarily solely, directed in activity to the vascular system and preferably peptides with CGRP antagonist activity," and, further, the "term 'vasoactive peptide' refers to peptides that are capable of causing vasoconstriction or vasodilation,"(see p. 8, lines 14). Thus, Applicants submit that the metes and bounds of the vasoactive peptides of the present invention are clear; vasoactive peptides include not only peptides that causes vasoconstriction or vasodilation, but also peptides that exert a physiological effect upon the caliber of blood vessels (see Dorland's Illustrated Medical Dictionary, a copy of which is enclosed herewith as Exhibit G). Furthermore, Applicants submit that a review of the technical literature, as previously presented in this communication makes it clear that the definition of "vasoactive" is well known in the art.

Applicants respectfully request the withdrawal of the rejection of claims 54 and 55 under 35 U.S.C. §112, second paragraph.

Claim Objections

The Examiner objected to claims 31 and 55. This objection is respectfully traversed.

Specifically, the Examiner objected to claim 31 for encompassing a non-elected species, SEQ ID NO:1. Claim 31, reciting elected species SEQ ID NO:2 and non-elected species SEQ ID NO:1, depends from generic claim 30, which depends from generic claim 29. With the

Office Action mailed April 8, 2003, the Examiner identified the allowance of claims 29 and 30. Thus, pursuant to MPEP § 8.01, "[u]pon the allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which are written in dependent form or otherwise include all the limitations of an allowed generic claim as provided by 37 CFR 1.141. Applicants respectfully request the withdrawal of the objection to claim 31 and the examination of the species SEQ ID NO:2.

Further, the Examiner objected to claim 55 as being in improper dependent form, for failing to further limit the subject matter of a previous claim. In support of this objection, the Examiner stated that "'Z' in the claim is defined as an antagonist of CGRP. As claim 55 depends from claim 54, in which Z is defined as a vasoactive peptide, it is not further limiting claim 54. . . . [as] an antagonist of CGRP is not vasoactive" (see page 2 of Office Action mailed April 8, 2003). Applicants respectfully disagree. First, Applicant's respectfully note that claim 55 recites "wherein Z is an antagonist of ***human*** CGRP" (emphasis added), and not "wherein Z is an antagonist of CGRP," as asserted by the Examiner. Second, as Applicants have presented in the paragraphs above, the Examiner's assertion that "an antagonist of CGRP is not vasoactive" is incorrect. Thus, Applicants submit that claim 55 properly limits claim 54, from which it depends.

In view of the above discussion, withdrawal of this objection to the claims is respectfully requested.

Summary

It is respectfully submitted that the pending claims 21-26, 29-47, 54, and 55 are in condition for allowance and notification to that effect is respectfully requested. The Examiner is invited to contact Applicants' Representatives, at the below-listed telephone number, if it is believed that prosecution of this application may be assisted thereby.

Respectfully submitted for

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By: Kelly A McAuley
Printed Name: Kelly A. McAuley

APPENDIX A - SPECIFICATION/CLAIM AMENDMENTS
INCLUDING NOTATIONS TO INDICATE CHANGES MADE
Serial No.: 09/813,345
Docket No.: 180.0002 0102

Amendments to the following are indicated by underlining what has been added and bracketing what has been deleted.

In the Claims

For convenience, all pending claims are shown below.

21. The method of Claim 29 wherein the CGRP receptor is on a cell.

22. The method of Claim 29 wherein the CGRP receptor is cell free.

23. The method of Claim 21 wherein the cell is in culture.

24. The method of Claim 21 wherein the cell is part of a tissue.

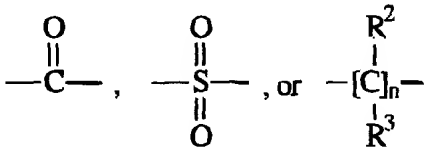
25. The method of Claim 21 wherein the cell is in an animal.

26. The method of Claim 25 wherein the animal is a human.

29. A method for inhibiting CGRP binding to one or more CGRP receptors comprising contacting a CGRP receptor with a composition comprising a peptide having the general formula:

$$R^1\text{-}X\text{-}Z$$

wherein Z is a CGRP receptor-binding peptide, R^1 is an organic group, X is



and wherein R^2 and R^3 are independently H or an organic group and n is a whole integer between 1 and 10;

in an amount effective to inhibit CGRP binding to one or more CGRP receptors.

30. The method of Claim 29 wherein Z is a peptide fragment of at least 15 amino acids from CGRP.

31. The method of Claim 30 wherein Z comprises the amino acid sequence of SEQ ID NO:1 or SEQ ID NO:2.

32. The method of Claim 29 wherein Z is an antagonist of human CGRP.

33. The method of Claim 29 wherein Z is an antagonist of α-CGRP or β-CGRP.

34. The method of Claim 33 wherein Z comprises the amino acid sequence of SEQ ID NOS:6-17 and 23.

35. The method of Claim 33 wherein Z comprises the amino acid sequence of SEQ ID NOS:18-22.

36. The method of claim 29 wherein Z is a CGRP antagonist peptide fragment selected from the group consisting of amylin, CGRP and adrenomedullin.

37. The method of Claim 29 wherein R^1 is an aromatic group, a heterocyclic group or an alkyl group and R^2 and R^3 are independently H, an aromatic group or an alkyl group.

38. The method of Claim 37 wherein R^1 is a C1-C4 alkyl group.

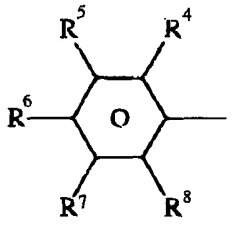
39. The method of Claim 38 wherein R^1 is a fluoroalkyl.

40. The method of Claim 38 wherein R^2 and R^3 are independently H, a C1-C4 alkyl group or a phenyl moiety.

41. The method of Claim 38 wherein R^1 is a C5-C10 aromatic group, a C5-C9 heterocyclic group or a C1-C4 alkyl group.

42. The method of Claim 41 wherein R^2 and R^3 are independently H or a C5-C10 aromatic group or a C1-C4 alkyl group.

43. The method of Claim 37 wherein R^1 has the general formula:



and wherein R^4-R^8 are each independently selected from the group of H, fluoro, chloro, bromo, iodo, nitro, nitrile (cyano), amino, N-methyl amino, N,N-dimethyl amino, hydroxy, methoxy, thiomethoxy (S-methyl), methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl, tert-butyl, trifluoromethyl, trifluoromethoxy, vinyl, acetamido, phenyl, toluyl, and methoxyphenyl.

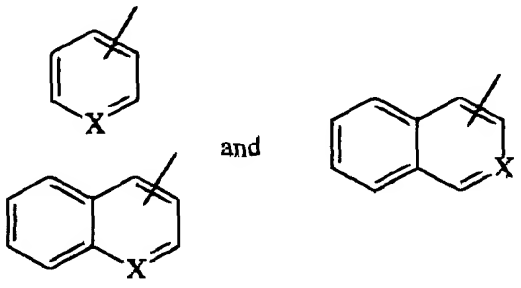
44. The method of Claim 43 wherein R^6 is trifluoromethyl and R^4, R^5, R^7 and R^8 are F.

45. The method of Claim 37 wherein R^1 is

and wherein Y is selected from the group consisting of O, NH, and S.

46. The method of Claim 43 wherein the peptide is a CGRP antagonist having at least 15 consecutive amino acids selected from a protein from the group consisting of N-α-benzoyl-α-CGRP, N-α-benzyl-β-CGRP, N-α-benzoyl-β-CGRP and N-α-benzyl-α CGRP, dibenzyl-h-α-CGRP and dibenzyl-h-β-CGRP.

47. The method of Claim 37 wherein R^1 is selected from the group consisting of:



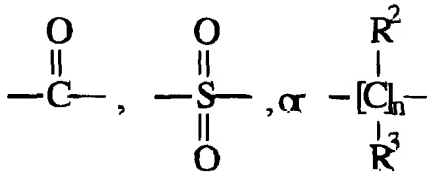
and wherein X is selected from the group consisting of C and N.

48. [Cancel] An assay for identifying CGRP antagonists comprising:

combining a peptide having the general formula:

$$R^1\text{-}X\text{-}Z$$

wherein Z is a CGRP receptor-binding peptide, R^1 is an organic group, X is



and whercin R^2 and R^3 are independently H or an organic group and n is a whole integer between 1 and 10, with at least one CGRP receptor and a test CGRP antagonist with at least one CGRP receptor; and

comparing binding of the peptide to the CGRP receptor with binding of the test antagonist to the CGRP receptor, wherein improved binding of the test antagonist to the CGRP receptor in the presence of the peptide identifies a candidate CGRP antagonist.

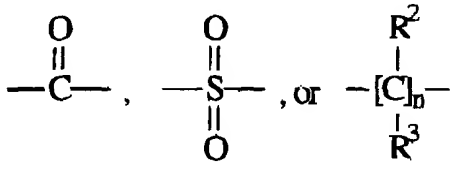
49. [Cancel] The assay of claim 48 wherein Z is a peptide fragment of at least 15 amino acids from CGRP.

50. [Cancel] The assay of claim 48 wherein Z is an antagonist of human CGRP.

51. [Cancel] A method for identifying a CGRP receptor in a cell sample comprising:
contacting a peptide having the general formula:

$$R^1\text{-}X\text{-}Z$$

wherein Z is a CGRP receptor-binding peptide, R^1 is an organic group, X is



and wherein R^2 and R^3 are independently H or an organic group and n is a whole integer between 1 and 10, with a cell sample to detect binding of the peptide to the cell; and isolating one or more receptors binding the peptide to the cell.

52. [Cancel] The assay of claim 51 wherein Z is a peptide fragment of at least 15 amino acids from CGRP.

53. [Cancel] The assay of claim 51 wherein Z is an antagonist of human CGRP.

54. The method of claim 29 wherein Z is a vasoactive peptide.

55. The method of claim 54 wherein Z is an antagonist of human CGRP.

EXHIBIT A

OMB No. 0651-0011

INFORMATION DISCLOSURE STATEMENT	Atty. Docket N .: 180.0002 0102	Serial No.: unknown; (parent: 09/070,504)
	Applicant(s): Derek D. SMITH et al.	
	Filing Date: herewith	Group:

DJ			Franc-Cereceda et al., "Calcitonin gene-related peptide but not substance P mimics capsaicin-induced coronary vascodilation in the pig", *Eur. J. Pharmacol.* 142: 235-243, 1987.
			Gardiner et al., "Antagonistic Effect of Human α-Calcitonin Gene-Related Peptide (8-37) on Regional Hemodynamic Actions of Rat Islet Amyloid Polypeptide in Conscious Long-Evans Rats", *Diabetes* 40:948-951, 1991.
			Griffin et al., "Effect of Endotoxicosis on Plasma and Tissue Levels of Calcitonin Gene-Related Peptide", *Circ. Shock* 38:50-54, 1992
			Huttemeier, et al., "Calcitonin gene-related peptide mediates hypotension and tachycardia in endotoxic rats", *Am. J. Physiol.* 265:H767-H769, 1993.
			Jansz, et al., "Identification and Partial Characterization of the Salmon Calcitonin/CGRP Gene by Polymerase Chain Reaction", *Ann. N. Y. Acad. Sci.* 657:63-69, 1992
			Jian et al., "Calcitonin Gene-Related Peptide in the Pathogenesis and Treatment of Hypertension", *Chinese Medical Journal* 102(12):897-901, 1989.
			Joyce et al., "Calcitonin gene-related peptide levels are elevated in patients with sepsis", *Surgery* 108:1097-1101, 1990.
			Kimura, S. et al., "Isolation and Amino Acid Sequence of Calcitonin Gene Related Peptide From Porcine Spinal Cord", *Neuropeptides* 9:75-82, 1987.
			Kitamura et al., "Adrenomedullin: A Novel Hypotensive Peptide Isolated from Human Pheochromocytoma", *Biochemical and Biophysical Research Commuications*, 192:553-560 1993.
			Leffert, J.D. et al., "Rat amylin: Cloning and tissue-specific expression in pancreatic islets", *Proc. Natl. Acad. Sci. USA* 86:3127-3130, 1989.
			Ling et al., "Synthesis of Antigenic Determinant Tyr-CGRP=(27~37) of Calcitonin Gene-Related Peptide," *Chinese Journal of Medicinal Chemistry*, 4(2):131-136 (1994).
		C	~~Ling et al., ""Synthesis of Antigenic Determinant Tyr-CGRP=(27~37) of~~ Calcitonin Gene-Related Peptide," *Chemical Abstracts*, *122*(15):1117, Abstract No. 122:188122f (1995).
DJ			Partial English-language translation of Ling et al., "Synthesis of Antigenic Determinant Tyr-CGRP=(27~37) of Calcitonin Gene-Related Peptide," *Chinese Journal of Medicinal Chemistry*, 4(2):131-136 (1994).

EXAMINER Dong Jiang	Date C nsidered 9/16/02

*Examiner: Initial if reference considered, whether or not citation is in conformance with MPEP 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

UME 122 CODEN: CHABA8 122(15) 1-1123 (1995) NUMBER 15
ISSN: 0009-2258

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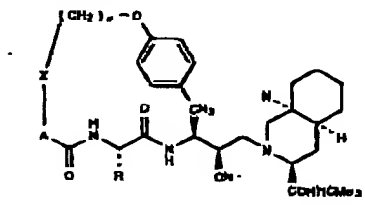
and no interresidue ROE cross-peaks except for the sequential backbone signals. These results were as expected for a random coil conformation. Conversely, II gave NMR spectra with indications of a bias toward defined secondary structures in soln. Computer-assisted mol. simulations were carried out to visualize these conformational biases. The rigidly oriented side chains of the (E)-cyclo-Met deriv. (wherein the α-amino group and the side chain are trans with respect to the cyclopropane ring) had a more severe effect on the allowable ψ values than on the φ torsions. The lowest energy structures generated in the dynamics run after minimization were grouped into families to give representations of related conformers. Finally, the results from the NMR and QMD studies were compared. For II, a good correlation was found, indicating a bias toward a γ-turn structure in soln. We predict that (E)-cyclo-Met residues in larger peptides could induce formation of turn or 3₁₀-helical structures.

122: 188119k **A new convenient route for the synthesis of DOPA peptides.** Nakonieczna, Lucja; Przychodzen, Witold; Chimiak, Andrzej (Fac. Org. Chem., Technical Univ. Gdansk, 80-952 Gdansk, Pol.). *Liebigs Ann. Chem.* 1994, (10), 1055-8 (Eng). The tert-butyldimethylsilyl group is introduced as the catechol protective group for DOPA, Boc-DOPA, and DOPA esters. The protected Boc-DOPA and DOPA esters were used as the starting materials for the synthesis of protected N-terminal DOPA and C-terminal DOPA dipeptides. Optimal conditions for deprotection are presented. Acidolysis of the fully protected DOPA peptides gives the pure DOPA dipeptides quant. in one step.

122: 188120d **Design, synthesis, and activity of conformationally-constrained macrocyclic peptide-based inhibitors of HIV protease.** Smith, Roger A.; Coles, Peter J.; Chen, Jian Jeffrey; Robinson, Valerie J.; MacDonald, I. David; Carriere, Julie; Krantz, Allen (Syntex Res., Mississauga, ON Can.). *Bioorg. Med. Chem. Lett.* 1994, 4(18), 2217-22 (Eng). Conformationally-constrained



I

macrocyclic peptide-based hydroxyethylamines I (A = 2,3-naphthalenediyl, 1,2-phenylenediyl, X = O; A = CH:CH, CH_2CH_2, X = CH_2; R = CH_2CONH_2, $CHMe_2$; n = 2-4) with 17- to 19-membered ring systems, have been designed and synthesized as HIV protease inhibitors. Structure-activity relationships were consistent with mol. modeling studies, and certain cyclic inhibitors were developed with HIV protease IC_{50} values of ~1 nM, and antiviral activities (HIV-1/RF infected MT-2 cells) of EC_{50} = 4-8 nM.

122: 188121e **Synthesis of c-Myb protein (38-89)-NH_2 using a partially protected peptide thioester.** Zhang, Ruo-Heng; Xu, Xiao-Jie; Tang, You-Qi; Hojo, Hironobu; Aimoto, Saburo (Department of Chemistry, Peking University, Beijing, Peop. Rep. China 100871). *Sci. China, Ser. B* 1994, 37(8), 932-9 (Eng).

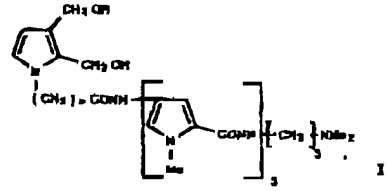
H-Leu-Gly-Lys-Thr-Arg-Trp-Thr-Arg-Glu-Glu-Asn-Glu-Lys-
Leu-Lys-Lys-Leu-Val-Gly-Glu-Asn-Gly-Thr-Asp-Asp-Trp
Lys-Val-Ile-Ala-Asn-Tyr-Leu-Pro-Asn-Arg-Thr-Asp-Val-
Gln-Cys-Gln-His-Arg-Trp-Glu-Lys-Val-Leu-Asn-Pro-Glu-NH_2 I

The method of selective modification of cysteine SH group with 4-methylbenzylchloride was developed. c-Myb protein (38-89)-NH_2 I was synthesized by using a partially protected peptide thioester. The 4-methylbenzyl protecting group of cysteine in the building block is stable during the segment coupling. The method can be used in the chem. synthesis of some protein contg. cysteine.

122: 188122f **Synthesis of antigenic determinant Tyr-CGRP(27-37) of calcitonin gene-related peptide.** Ling, Yun; Rong, Yang; Lu, Miaoru; Hu, Xinoyu (Dep. Cent. Lab., Naval General Hosp., Beijing, Peop. Rep. China 100037). *Zhongguo Yaowu Huaxue Zazhi* 1994, 4(2), 131-3, 136 (Ch). By use of MBHA resin and Boc strategy antigenic determinant Tyr-CGRP(27-37) of calcitonin gene-related peptide (CGRP) was synthesized by Merrifield solid phase synthesis. Hydroxy groups in Ser, Thr and Tyr were protected with benzyl groups, the amino group of Lys was protected with Cl-Z. The structure of Tyr-CGRP(27-37) was confirmed on the basis of FAB-MS and amino acid anal.

122: 188123g **Synthesis and conformational studies of peptides containing TOAC, a spin-labeled $C^{\alpha\alpha}$-disubstituted glycine.** Toniolo, Claudio; Valente, Ezio; Formaggio, Fernando; Crisma, Marco; Pilloni, Giuseppe; Corvaja, Carlo; Toffoletti, Antonio; Martinez, Gary V.; Hanson, M. Paul; *et al.* (Department of Organic Chemistry, University of Padova, 35131 Padua, Italy). *J. Pept. Sci.* 1995, 1(Launch Issue), 45-67 (Eng). A variety of host L-alanine homopeptides (to the pentamer) contg. one or two spin-labeled 2,2,6,6-tetramethylpiperidine-1-oxyl-4-amino-4-carboxylic acid (TOAC) residues were synthesized by soln. methods and fully characterized. The conformational features of the terminally blocked, doubly spin-labeled pentapeptide 4-$Br C_6H_4CO$-TOAC-(Ala)$_3$-TOAC-Ala-$NHCMe_2$ were examd. by x-ray crystallog. and in soln. using a combination of techniques (Fourier transform IR, CD, cyclic voltammetry, and ESR) in comparison with singly labeled shorter peptides. The 3₁₀-helical structure of the pentapeptide, promoted by the two C^{α}-disubstituted glycines under favorable exptl. conditions, allows an interaction to take place between the two nitroxide TOAC side chains spaced by one turn of the helix. Taken together, these results suggest that TOAC is an excellent probe for exploring bends and helixes in doubly labeled peptides.

122: 188124h **Synthesis and reactions with DNA of a family of DNA-DNA affinity crosslinking agents.** Sugurdsson, Snorri Th.; Hopkins, Paul B. (Dep. Chem., Univ. Washington, Seattle, WA 98195 USA). *Tetrahedron* 1994, 50(42), 12065-84 (Eng).



I

DNA-DNA crosslinking agents I [n = 2-4] were prepd. These substances were efficient, sequence selective, DNA-DNA interstrand and intrastrand crosslinking agents. I [n = 2] formed interstrand and intrastrand cross-links at the sequences 5'-d:CGAATT) and 5'-d(GGAATT), resp. The lesions from hydrolysis of the phosphodiester backbones of inter- and intrastrand cross-linked DNA were identical. I [n = 2] was 1000-fold more active as a crosslinking agent than 2,3-bis-(hydroxymethyl)-1-methypyrrole. The cytotoxicity of I [n = 3] was comparable to cis-DDP.

122: 188125j **The use of HMOC-TOCSY experiments for elucidating the structures of bicyclic lactams: uncovering a surprise rearrangement in the synthesis of a key Pro-Phe building block.** Moeller, Keven D.; Hanau, Catheleen E.; d'Avignon, Andre (Dep. Chemistry, Washington Univ., St. Louis, MO 63130 USA). *Tetrahedron Lett.* 1994, 35(6), 825-8 (Eng). HMQC-TOCSY expts. were used to unequivocally assign the ring skeletons of several bicyclic lactams. This work demonstrated the power of these techniques for establishing the complete carbon connectivity of peptide building blocks with closely overlapping protons. In addn., it has led to the discovery of a surprise rearrangement reaction and allowed for the correction of a previously misassigned Pro-Phe building block ring skeleton.

122: 188126k **Muramyl peptide analogs: synthesis of a depsipeptide using orthogonal SPPS.** Cunningham, Barry R.; Hannah, John; Jones, A. Brian (Dep. Synthetic Chemical Research, Merck Research Laboratories, Rahway, NJ 07065 USA). *Tetrahedron Lett.* 1994, 35(51), 9517-20 (Eng). A depsipeptide mimic of the Gram-pos. muramyl peptide was synthesized on resin using both Boc and Fmoc protection strategies. The depsipeptide unit is chem. and stereochem. compatible with both Boc and Fmoc chemistries and with HF cleavage conditions.

122: 188127m **Synthesis of activated disulfide adducts containing a 4-diazocyclohexa-2,5-dienone precursor for photoaffinity labeling.** Dugave, Christophe; Kessler, Pascal (Departement d-Ingenierie et d-Etude des Proteines (DIEP), CEA, 91191 Yvette, Fr.). *Tetrahedron Lett.* 1994, 35(51), 9557-60 (Eng). New activated disulfides bearing a 4-diazocyclohexa-2,5-dienone precursor were synthesized in order to build up photoactivable and cleavable peptides via cysteine modification.

122: 188128n **(η⁴-Cyclopentadienyl)Fe(CO)₂-complex of Maleimide as an organometallic carbonyl probe for biomolecules containing HS groups.** Rudolf, Bogna; Zakrzewski, Janusz (Dep. Organic Chem., Univ. Lodz, 68 Narutowicza, Pol.). *Tetrahedron Lett.* 1994, 35(51), 9611-12 (Eng). Synthesis of (η⁵-cyclopentadienyl)Fe(CO)₂(η¹-maleimidato) complex and its reaction with L-cysteine Et ester hydrochloride and glutathione are reported. This reaction enables introduction of a metal carbonyl probe into biomols. contg. HS groups.

122: 188129p **Use of 1-β-naphthalenesulfonyloxybenzotriazole as coupling reagent in solid phase peptide synthesis.** Kundu, Bijoy; Shukla, Sushma; Shukla, Manisha (Division Biopolymers, Central Drug Research Institute, Lucknow, 226001 India). *Tetrahedron Lett.* 1994, 35(51), 9613-16 (Eng). Application of 1-β-naphthalenesulfonyloxybenzotriazole (NSBt) as an efficient coupling reagent in solid phase is reported. It has been suitable for the rapid and quant. coupling of various amino acid derivs.

122: 188130g **Solid-phase synthesis of "head-to-tail" cyclic peptides via lysine side-chain anchoring.** Alsina, Jordi; Rabanal, Francesc; Giralt, Ernest; Albericio, Fernando (Dep. Organic Chem., Univ. Barcelona, Barcelona, Spain E-08028). *Tetrahedron Lett.* 1994, 35(51), 9633-5 (Eng). The N,N'-disuccinimidyl carbonate (DSC) has been successfully used for the efficient conversion of conventional hydroxymethyl resins into active carbonate resins, which are suitable for the incorporation of protected amino acids via an amino function, allowing the prepn. of "head-to-tail" cyclic lysine contg. peptides.

122: 188131h **Synthesis of the fragments of melittin and their interaction with calmodulin.** Liu, Li-ping; Yan, Hu-sheng; Ni, Ai-guo; Cheng, XiO-hui; He, Bing-lin (Inst. Polymer Chem., Nankai Univ., Tianjin, Peop. Rep. China 300071). *Shengwu Huaxue Zazhi* 1994, 10(6), 651-6 (Ch). Four fragments of melittin, Mel 12, Mel 13, Mel 14 and Mel 15, were manually synthesized by std. solid-phase method. Their interaction with calmodulin was studied by electrophoresis method, inhibited activity of Ca^{2+}-dependent 3',5'-cAMP phosphodiesterase and fluorescence technique. The

EXHIBIT B

STEDMAN'S Medical Dictionary

27th Edition

Illustrated in Color

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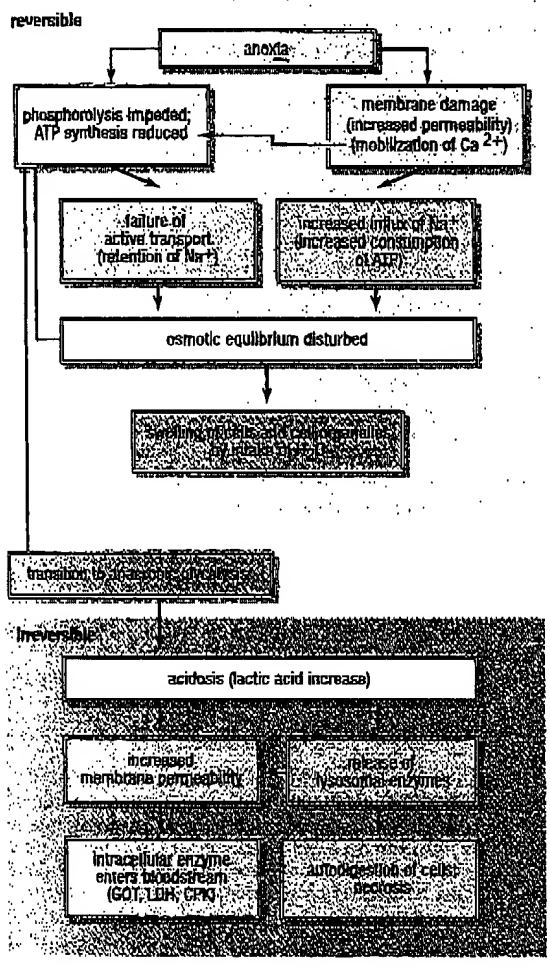

anoxia: pathogenesis of anoxic cell destruction; ATP, adenosine 5'-triphosphate; GOT, glutamic-oxaloacetic transaminase; LDH, lactate dehydrogenase; CPK, creatine phosphokinase

Anrep, G.V., 20th century Lebanese physiologist in Britain. SEE A. *phenomenon*.

ANS Abbreviation for anterior nasal *spine*; autonomic nervous *system*.

an·sa, gen. and pl. **an·sae** (an′să, -sē) [TA]. Any anatomical structure in the form of a loop or an arc. SEE ALSO loop. [L. loop, handle]

a. cervica′lis [TA], a loop in the cervical plexus consisting of fibers from the first three cervical nerves. Fibers from a loop between the C1 and C2 spinal nerves accompany the hypoglossal nerve for a short distance, leaving it as the superior root of the a. cervicalis. Fibers from a loop between the C2 and C3 spinal nerves form the inferior root of the a. cervicalis. Most commonly, the roots merge, forming the a. cervicalis, which gives rise to branches innervating infrahyoid muscles. SYN cervical loop, loop of hypoglossal nerve.

Haller a., SYN communicating *branch* of facial nerve with glossopharyngeal nerve.

Henle a., SYN nephronic *loop*.

a. hypoglos′si, obsolete term for a. cervicalis.

lenticular a., SYN lenticular *loop*.

a. lenticula′ris [TA], SYN lenticular *loop*.

ansae nervo′rum spina′lium, SYN *loops* of spinal nerves, under *loop*.

peduncular a., SYN a. peduncularis.

a. peduncula′ris [TA], a complex fiber bundle curving around the medial edge of the internal capsule and connecting the anterior part of the temporal lobe (temporal cortex), amygdala, and olfactory cortex with the mediodorsal nucleus of the thalamus; it enters the thalamus as a component of the inferior thalamic peduncle which also contains a major part of the fibers connecting the mediodorsal nucleus to the orbitofrontal cortex. SYN peduncular a., peduncular loop, Reil a.

Reil a., SYN a. peduncularis.

a. sacra′lis, a nerve cord connecting one or both of the sympathetic nerve trunks with the ganglion impar.

a. subcla′via [TA], a nerve cord connecting the middle cervical and inferior cervical or stellate sympathetic ganglia, forming a loop around the subclavian artery. SYN subclavian loop, Vieussens a., Vieussens loop.

Vieussens a., SYN a. subclavia.

an·sate (an′sāt). SYN ansiform.

an·ser·ine. **1** (an′ser-īn). Resembling or characteristic of a goose. SEE *cutis* anserina, *pes* anserinus. **2** (an′ser-ēn). *N*ᵅ-(β-Alanyl)-π-methyl-L-histidine; present in muscle and brain. SYN *N*-methylcarnosine. [L. *anserinus*, fr. *anser*, goose]

ANSI Abbreviation for American National Standards Institute.

an·si·form (an′si-fōrm). In the shape of a loop or arc. SYN ansate. [L. *ansa*, handle, + *forma*, shape]

an·sot·o·my (an-sot′ŏ-mē). **1.** Surgical division of a loop, usually a constricting loop. **2.** Section of the ansa lenticularis for treatment of striatal syndromes. [L. *ansa*, handle + G. *tomē*, cutting]

ant-. SEE anti-.

ant. One of the most numerous insects (order Hymenoptera), characterized by an extraordinary development of colonial dwelling and caste specialization.

black imported fire a., SYN *Solenopsis richteri*.

fire a., any of several species in the genus *Solenopsis* whose bite causes a fiery, burning sensation and sometimes severe allergic reactions. SEE ALSO solenopsin A.

harvester a., SYN *Pogonomyrmex*.

red imported fire a., SYN *Solenopsis invicta*.

velvet a., a wingless mutilid wasp (family Mutilidae, order Hymenoptera) known for its venomous sting.

ant·ac·id (ant-as′id). **1.** Neutralizing an acid. **2.** Any agent that reduces or neutralizes acidity, as of the gastric juice or any other secretion (e.g., calcium carbonate, magnesium hydroxide). SYN antiacid.

an·tag·o·nism (an-tag′on-izm). **1.** Denoting mutual opposition in action between structures, agents, diseases, or physiologic processes. Cf. synergism. **2.** The situation in which the combined effect of two or more factors is smaller than the solitary effect of any one of the factors. SYN mutual resistance. [G. *antagōnisma*, from *antí*, against, + *agōnizomai*, to fight, fr. *agōn*, a contest]

bacterial a., the inhibition of one bacterium by another

an·tag·o·nist (an-tag′ŏ-nist). Something opposing or resisting the action of another; certain structures, agents, diseases, or physiologic processes that tend to neutralize or impede the action or effect of others. Cf. synergist.

α-adrenoceptor a., SYN α-adrenergic blocking *agent*.

β-adrenoreceptor a., SYN β-adrenergic blocking *agent*.

aldosterone a., an agent that opposes the action of the adrenal hormone aldosterone on renal tubular mineralocorticoid retention; these agents, e.g., spironolactone, are useful in treating the hypertension of primary hyperaldosteronism, or the sodium retention of secondary hyperaldosteronism.

associated a., one of two muscles or groups of muscles which pull in nearly opposite directions, but which, when acting together, move the part in a path between their diverging lines of action.

calcium a., SYN calcium channel-blocking *agent*.

competitive a., an antimetabolite.

enzyme a., an antimetabolite or inhibitor of enzyme action.

folic acid a.'s, modified pterins, such as aminopterin and methotrexate, that interfere with the action of folic acid and thus pro-

duce the symptoms of folic acid deficiency; have been used in cancer chemotherapy and inflammatory disorders.

5-hydroxy tryptamine a.'s, agents that block serotonin receptors and hence interfere with the biological actions of serotonin (5-HT).

insulin a., substances in the β- and γ-globulin or β_1-lipoprotein fractions of serum that may induce a functional insulin deficiency; may include nonprecipitating antibodies against nonhuman insulin.

leukotriene receptor a., a class of agents, of which zileuton, montelukast, zafirlukast are the best known, used in the prophylactic and chronic treatment of asthma in older children and adults; these drugs are not bronchodilators in themselves, but act by interfering with the leukotriene-mediated inflammatory process present in asthma.

muscarinic a., drugs that bind with muscarinic cholinergic receptors but do not activate them, thus preventing access to acetylcholine; examples include atropine, scopolamine, propantheline, and pirenzepine.

opioid a.'s, agents such as naloxone and naltrexone that have high affinity for opiate receptors but do not activate these receptors. These drugs block the effects of exogenously administered opioids such as morphine, heroin, meperidine, and methadone, or of endogenously released endorphins and enkephalins.

ant·al·ge·sia (ant-al-jē'zē-ă). Rarely used term for lowering of a previous elevation in pain threshold. [anti- + G. *algēsis*, sense of pain]

ant·al·gic (ant-al'jik). SYN analgesic (2).

ant·al·ka·line (ant-al'kă-līn). Reducing or neutralizing alkalinity.

ant·aph·ro·di·si·ac (ant'af-rō-diz'ē-ak). SYN anaphrodisiac.

ant·aph·ro·dit·ic (ant'af-rō-dit'ik). 1. SYN anaphrodisiac. 2. SYN antivenereal.

ant·ar·thrit·ic (ant'ar-thrit'ik). Rarely used term for: SYN antiarthritic.

ant·as·then·ic (ant-as-then'ik). 1. Strengthening or invigorating. 2. An agent possessing such qualities. [anti- + G. *astheneia*, weakness]

ant·asth·mat·ic (ant-az-mat'ik). SYN antiasthmatic.

ant·a·tro·phic (ant-ă-trof'ik). 1. Preventing or curing atrophy. 2. An agent that promotes the restoration of atrophied structures.

an·taz·o·line hy·dro·chlo·ride (an-taz'ō-lēn). A histamine-antagonizing agent used in treating allergy; also available as a. h. phosphate. SYN phenazoline hydrochloride.

ante-. Before, in front of (in time or place or order). SEE ALSO pre-, pro- (1). [L. *ante*, before, in front of]

an·te·brach·i·al (an'te-brā'kē-ăl). Relating to the forearm.

an·te·bra·chi·um (an-te-brā'kē-ŭm) [TA]. SYN forearm. [ante- + L. *brachium*, arm]

an·te·car·di·um (an-te-kar'dē-ŭm). SYN precordia.

an·te·ced·ent (an-te-sē'dent). A precursor. [L. *antecedo*, to go before]

plasma thromboplastin a. (PTA), SYN *factor* XI.

an·te ci·bum (an'tē sī'bŭm). Before a meal. The plural is ante cibos, before meals. [L.]

an·te·cu·bi·tal (an-te-kū'bi-tăl). In front of the elbow. [ante- + L. *cubitum*, elbow]

an·te·fe·brile (an-te-feb'ril). Rarely used term for antepyretic. [ante- + L. *febris*, fever]

an·te·flex (an'te-fleks). To bend anteriorly (forward) or cause to bend anteriorly. [ante- + L. *flecto*, pp. *flexus*, to bend]

an·te·flex·ion (an-te-flek'shŭn). A bending forward; a sharp forward curve or angulation; denoting especially the normal forward bend in the uterus at the junction of corpus and cervix uteri.

a. of iris, rarely used term for an iris that is, in part, folded forward after a severe iridodialysis so that the pigmented layer faces forward.

an·te·grade (an'tē-grād). In the direction of normal movement, as in blood flow or peristalsis. [ante- + L. *gradior*, to walk]

an·te·mor·tem (an'te-mōr-tem). Before death. Cf. postmortem. [ante- + L. *mors* (*mort-*), death]

an·te·na·tal (an-te-nā'tăl). SYN prenatal. [ante- + L. *natus*, birth]

an·te·par·tum (an'te-par-tŭm). Before labor or childbirth. Cf. intrapartum, postpartum. [ante- + L. *pario*, pp. *partus*, to bring forth]

an·te·po·si·tion (an'te-pō-si'shŭn). Forward or anterior position.

an·te·py·ret·ic (an'te-pī-ret'ik). Before the occurrence of fever; before the period of reaction following shock. [ante- + G. *pyretos*, fever]

an·te·ri·or (an-tēr'ē-ōr). 1 [NA]. In human anatomy, denoting the front surface of the body; often used to indicate the position of one structure relative to another, i.e., situated nearer the front part of the body. SYN ventral (2) [TA], ventralis [TA]. 2. Near the head or rostral end of certain embryos. 3. Undesirable and confusing substitute for *cranial* in quadrupeds. In veterinary anatomy, a. is restricted to parts of the eye and inner ear. 4. Before, in relation to time or space. [L.]

antero-. Anterior. [L. *anterior*, more before, earlier, fr. *ante*, before, + -r- *-ior*, more]

an·ter·o·ex·ter·nal (an'ter-ō-eks-ter'năl). In front and to the outer side.

an·ter·o·grade (an'ter-ō-grād). 1. Moving forward. Cf. antegrade. 2. Extending forward from a particular point in time; used in reference to amnesia. [L. *gradior*, pp. *gressus*, to step, go]

an·ter·o·in·fe·ri·or (an'ter-ō-in-fēr'ē-ōr). In front and below.

an·ter·o·in·ter·nal (an'ter-ō-in-ter'năl). In front and to the inner side.

an·ter·o·lat·er·al (an'ter-ō-lat'er-ăl). In front and away from the middle line.

an·ter·o·me·di·al (an'ter-ō-mē'dē-ăl). In front and toward the middle line.

an·ter·o·me·di·an (an'ter-ō-mē'dē-an). In front and in the central line.

an·ter·o·pos·te·ri·or (an'ter-ō-pos-tēr'ē-er). 1. Relating to both front and rear. 2. In x-ray imaging, describing the direction of the beam through the patient (projection) from anterior to posterior, e.g., an A-P projection of the abdomen; or the direction of view (A-P view) when a film is viewed as if facing the patient (anterior to posterior) regardless of projection.

an·ter·o·su·pe·ri·or (an'ter-ō-soo-pē'rē-er). In front and above.

ant·e·rot·ic (ant-er-ot'ik). Pertaining to an effort to avoid erotic feelings. [anti- + G. *erōtikos*, pertaining to love]

an·te·sys·to·le (an-te-sis'tō-lē). Premature activation of the ventricle responsible for the pre-excitation syndrome of the Wolff-Parkinson-White or Lown-Ganong-Levine types.

an·te·ver·sion (an-te-ver'shŭn). Turning forward, inclining forward as a whole without bending. [ante- + Mediev. L. *versio*, a turning]

an·te·vert·ed (an-te-vert'ed). Tilted forward; in a position of anteversion.

ant·hel·ix (ant'hē-liks, an'thē-liks). SYN antihelix. [anti- + G. *helix*, coil]

ant·hel·min·thic (ant-hel-min'thik). SYN anthelmintic (1).

ant·hel·min·tic (ant-hel-min'tik, an-thel-). 1. An agent that destroys or expels intestinal worms. SYN anthelminthic, antihelminthic, helminthagogue, helminthic (2), helmintic (2), vermifuge. 2. Having the power to destroy or expel intestinal worms. SYN vermifugal. [anti- + G. *helmins*, worm]

an·the·lone (an'thē-lōn). SYN urogastrone.

a. E, SYN enterogastrone.

a. U, SYN urogastrone.

an·ther·id·i·um (an'ther-id'ē-um). The male gametangium produced in the teleomorph part of the life cycle of fungi. [Mod. L. *anthera*, flower, fr. G *antherōs*, blooming, fr. *anthēo*, to bloom, + dim. suffix *-idium*, fr. G. *-idion*]

an·thi·o·li·mine (an-thī-ō'li-mēn). Used in the treatment of filariasis and schistosomiasis.

an·tho·cy·a·nins (an-thō-sī'ă-ninz). A group of floral pigments, existing as glycosides in combination with glucose or cellobiose molecules, that range from red to blue and are often pH dependent; soluble in water and alcohol but not in ether. A. are

EXHIBIT C

Search or Browse?

Different types of questions require different methods of research.

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Merriam-Webster's Collegiate Dictionary

Search [redacted]

Main Entry: an·tag·o·nist
Pronunciation: -nist
Function: *noun*
Date: 1594
1 : one that contends with or opposes another : ADVERSARY, OPPONENT
2 : an agent of physiological antagonism: as a : a muscle that contracts with and limits the action of an agonist with which it is paired -- called also *antagonistic muscle* b : a chemical that acts within the body to reduce the physiological activity of another chemical substance (as an opiate); *especially* : one that opposes the action on the nervous system of a drug or a substance occurring naturally in the body by combining with and blocking its nervous receptor -- compare AGONIST 2b

Dictionary Pronunciation Key

\&\ as a and u in abut	\e\ as e in bet	\o\ as aw in law
\[^&]\ as e in kitten	\E\ as ea in easy	\oi\ as oy in boy
\&r\ as ur and er in further	\g\ as g in go	\th\ as th in thin
\a\ as a in ash	\i\ as i in hit	\[th_]\ as th in the
\A\ as a in ace	\I\ as i in ice	\ü\ as oo in loot
\ä\ as o in mop	\j\ as j in job	\u\ as oo in foot
\au\ as ou in out	\[ng]\ as ng in sing	\y\ as y in yet
\ch\ as ch in chin	\O\ as o in go	\zh\ as si in vision

EXHIBIT D

Drug-Receptor Interactions

The Merck Manual of Diagnosis and Therapy
Section 22. Clinical Pharmacology
Chapter 300. Pharmacodynamics

Topics

navigation help

Few if any drugs have absolute specificity, but most have relative selectivity; eg, atropine inhibits the actions of acetylcholine on exocrine glands and smooth muscles, but not on skeletal muscle. The action of such selective drugs results from their physicochemical binding to cellular components called receptors. Physiologic receptors are macromolecules involved in chemical signaling between and within cells. A molecule that binds to a receptor is called a ligand. When a ligand (hormone, neurotransmitter, intracellular messenger molecule, or exogenous drug) combines with a receptor, cell function changes (see Table 300-1). Each ligand may interact with multiple receptor subtypes. Activated receptors directly or indirectly regulate cellular biochemical processes (eg, ion conductance, protein phosphorylation, DNA transcription). In many cases, receptors within the cell membrane are coupled through guanine nucleotide-binding proteins (G proteins) to various effector systems involving intracellular second messenger molecules.

Receptors are dynamic, influenced by external factors as well as by intracellular regulatory mechanisms. Receptor up-regulation and down-regulation are relevant to clinically important adaptation to drugs (desensitization, tachyphylaxis, tolerance, acquired resistance, postwithdrawal supersensitivity).

Recognition sites are the precise molecular regions of receptor macromolecules to which ligands bind. A drug may interact at the same site as an endogenous agonist (hormone or neurotransmitter) or at a different site. Agonists that bind to an adjacent or a different site are sometimes termed allosteric agonists. Nonspecific drug binding also occurs--ie, at molecular sites not designated as receptors (eg, plasma proteins).

Drug receptor theory, grounded in the law of mass action, is somewhat comparable to kinetic analyses of enzyme-substrate interaction and inhibition. Many biochemical mechanisms of drugs can be studied within this reference frame (eg, aspirin-prostaglandin synthetase inhibitor, neostigmine-cholinesterase inhibitor, deprenyl-monoamine oxidase B inhibitor). Drug receptor theory includes the concepts of **affinity** (the probability of the drug occupying a receptor at any given instant) and **intrinsic efficacy** (intrinsic activity), which expresses the complex associations between drug or ligand concentration, activation states of receptors, and the cellular or tissue functional response.

Physiologic functions (eg, contraction, secretion) are regulated by multiple receptor-

mediated mechanisms and consequently can be modulated by dissimilar molecular stimuli. Several steps (eg, involving receptor-coupling and multiple intracellular second messenger substances) may be interposed between the initial molecular drug-receptor interaction and ultimate tissue or organ response. Receptor densities and efficiencies of stimulus-response mechanisms vary from tissue to tissue.

Early drug occupation theory assumed that a pharmacologic response was directly proportional to receptor occupancy; a maximal effect occurred when all receptors were occupied or activated. Current theory includes kinetic processes (onset/offset rates) of ligand-receptor occupancy, multiple activation states (active/inactive) of receptors, and the lack of apparent proportionality between ligand-receptor occupancy and ultimate tissue or organ response. In these models, variations in signal transduction efficiency (cell amplification mechanisms) and the existence of spare receptors, partial agonists, and inverse agonists (see below) are considered.

Agonist drugs interact with receptors to alter the proportion of activated receptors, thus modifying cellular activity. Conventional agonists increase the proportion of activated receptors; inverse agonists reduce it. Many hormones and neurotransmitters (eg, acetylcholine, histamine, norepinephrine) and many drugs (eg, morphine, phenylephrine, isoproterenol) act as agonists.

Antagonists interact selectively with receptors but do not lead to an observed effect; they reduce the action of another substance (agonist) at the receptor site involved. Receptor antagonists thus possess affinity but lack intrinsic efficacy.

Structural analogs of agonist molecules frequently have dual agonist and antagonist properties; such drugs are termed partial (low-efficacy) agonists. For example, isoproterenol is a full agonist and prenalterol is a partial agonist for β-adrenergic receptors in some tissues. A drug that acts as a partial agonist in one tissue may act as a full agonist i another.

Receptor antagonists can be classified as reversible or irreversible. Reversible antagonists readily dissociate from their receptor; irreversible antagonists form a stable chemical bond with their receptor (eg, in alkylation). Pseudoirreversible antagonists slowly dissociate fron their receptor. In competitive antagonism, the binding of agonist and antagonist is mutually exclusive, possibly because both agents bind to the same receptor site. In noncompetitive antagonism, agonist and antagonist can be bound simultaneously, but antagonist binding reduces or prevents the action of the agonist. In reversible competitive antagonism, agonist and antagonist form short-lasting combinations with the receptor, and steady state between agonist, antagonist, and receptor is reached. Such antagonism can be overcome by increasing the concentration of the agonist; ie, antagonism is surmountable. For example, naloxone--an opioid receptor antagonist structurally similar to morphine, with little or no morphine-like activity--blocks morphine's effects when given before or after morphine. However, competitive antagonism by naloxone can be overcome by giving more morphine

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The Merck Manual of Diagnosis and Therapy

Sections

Updates, Enhancements, and Changes

Purchasing Information
Home
Navigation Help

Foreword to the Print Edition

The Merck Manual of Diagnosis and Therapy
Front Matter
Topics
Foreword to the Print Edition
A Centennial History
Guide for Readers of the Internet Edition
Abbreviations and Symbols
Editors and Editorial Board
Consultants
Contributors
Editorial and Production Staff
navigation help

With this edition, *The Merck Manual* celebrates its 100th birthday. When the editors of the 1st Edition produced their 192-page compendium, they could not have realized the extent to which medical knowledge would explode over the next century. *The Merck Manual* now fills 2,655 pages and covers countless diseases that were not known 100 years ago. A brief review of medical practice as reflected in *The Merck Manual* during the past century follows in the section A Centennial History.

Although the knowledge of medicine has grown, the goal of *The Merck Manual* has not changed--To provide useful clinical information to practicing physicians, medical students, interns, residents, nurses, pharmacists, and other health care professionals in a concise, complete, and accurate manner. *The Merck Manual* continues to cover all the subjects expected in a textbook of internal medicine as well as detailed information on pediatrics, psychiatry, obstetrics, gynecology, dermatology, pharmacology, ophthalmology, otolaryngology, and a number of special subjects. *The Merck Manual* quickly provides information that helps practitioners achieve optimal care. The more specialized the practice of medicine becomes, the more important such information becomes. Specialists as well as generalists must at some time quickly access information about other specialties.

The 17th edition of *The Merck Manual* is the culmination of an arduous but rewarding 7-year enterprise. Every topic has been updated, and many have been completely rewritten. Topics new to this edition include hand disorders, prion diseases, death and dying, probabilities in clinical medicine, multiple chemical sensitivity, chronic fatigue syndrome, rehabilitation, smoking cessation, and drug therapy in the elderly, among others. The members of the Editorial Board, special consultants, and contributing authors are listed on the following pages with their affiliations. They deserve a degree of gratitude that cannot b adequately expressed here, but we know they will feel sufficiently rewarded if their efforts serve your needs.

Because of the extensive subject matter covered and a successful tradition developed through trials of successes and failures, *The Merck Manual* has some unique characteristics We urge readers to spend a few minutes reviewing the Guide for Readers.

We hope this edition of *The Merck Manual* will serve as an aid to you, our readers, compatible with your needs and worthy of frequent use. Suggestions for improvements wil be warmly welcomed and carefully considered.

Mark H. Beers, M.D., and Robert Berkow, M.D., *Editor*

[General]

Pharmacodynamics: Study of the biochemical and physiologic effects of drugs and their mechanisms of action.

Many drugs produce pharmacologic responses by interacting with (binding to) specific macromolecules, usually complex proteins, on or within cells. Some drug classes react directly with endogenous or exogenous nonprotein substances; included are some cancer chemotherapeutic drugs that interact with nucleic acids, metal chelating drugs (eg, calcium disodium edetate, dimercaprol, deferoxamine), and antacids used to chemically neutralize gastric acid.

Dose-Response Relationships

Correspondence between the amount of an administered drug and the magnitude of the evoked reaction.

Dose-response relationships are very important in therapeutic decisions and in experimental pharmacology. Dose-response data are typically graphed, with the measured effect (response) on the ordinate and the dose or function of dose (eg, $\log_{10}$ dose) on the abscissa. Because a drug effect is a function of both dose (or concentration) and time, such a graph depicts the dose-response relationship independent of time. Measured effects are frequently recorded as maxima at time of peak effect or under steady-state conditions (eg, during continuous IV infusion). Drug effects may be quantified at the level of molecule, cell, tissue, organ, organ system, or organism.

A hypothetical dose-response curve has variable features (see Fig. 300-1): potency (location of curve along the dose axis), maximal efficacy or ceiling effect (greatest attainable response), and slope (change in response per unit dose). Biologic variation (variation in magnitude of response among test subjects in the same population given the same dose of drug) also occurs. Graphing dose-response curves of drugs studied under identical conditions can help compare the pharmacologic profiles of the drugs (see Fig. 300-2).

EXHIBIT E

BIOCHEMICAL AND BIOPHYSICAL

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Volume 171, Number 3, September 28, 1990

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BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS
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Vol. 171, No.

ANTAGONISTIC EFFECT OF HUMAN α-CGRP [8-37] ON THE IN VIVO REGIONAL HAEMODYNAMIC ACTIONS OF HUMAN α-CGRP

S.M. Gardiner, A.M. Compton, P.A. Kemp, T. Bennett,
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* Celltech Ltd., Slough, SL1 4EN, U.K.

Received August 6, 1990

In conscious rats, infusion of human α-CGRP [8-37] (30 nmol/kg/min) caused small, reversible reductions in hindquarters flow and vascular conductance only, whereas at a dose of 300 nmol/kg/min there was a tachycardia and an increase in mean arterial blood pressure, together with renal, mesenteric and hindquarters vasoconstrictions. Human α-CGRP (0.03 nmol/kg/min) caused tachycardia, hypotension, and transient renal, but sustained hindquarters, vasodilatation; these changes were accompanied by mesenteric vasoconstriction. Infusion of human α-CGRP [8-37] (30 nmol/kg/min) during administration of human α-CGRP (0.03 nmol/kg/min) abolished the effects of the latter but these re-appeared when the human α-CGRP [8-37] infusion was stopped. This dose of human α-CGRP [8-37] did not affect cardiovascular responses to isoprenaline. These results indicate that human α-CGRP [8-37] is an effective antagonist of the cardiovascular actions of human α-CGRP in vivo.

Infusion of exogenous human α-CGRP has potent effects on regional haemodynamics in vivo (1,2), but our understanding of the possible physiological roles of endogenous CGRP in cardiovascular regulation has been hampered by the lack of an antagonist for this peptide. Although recent reports indicate that CGRP might interact with different receptors in different tissues (3), there is in vitro evidence that C-terminal fragments of human α-CGRP have antagonistic activity in various systems (3-7). Therefore, the objectives of the present work were to assess the in vivo haemodynamic effects of human α-CGRP [8-37] (5), and to determine if it antagonised the cardiovascular actions of human α-CGRP.

MATERIALS AND METHODS

Male, Long Evans rats (350-450g) were anaesthetised (sodium methohexitone, 60 mg/kg, supplemented as necessary) and had pulsed Doppler probes (8) implanted around the left renal and superior mesenteric arteries and the distal abdominal aorta to monitor hindquarters flow (1). Animals were given ampicillin (7 mg/kg i.m.) and returned to their home cages. At least 7 days later animals were briefly re-anaesthetised (sodium

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methohexitone 40 mg/kg i.p.) and had intravascular catheters implanted; experiments began the following day with rats fully conscious and unrestrained in their home cages. Continuous recordings were made of instantaneous heart rate, mean arterial blood pressure and Doppler shift signals from the renal, mesenteric and hindquarters probes.

In preliminary experiments we found that human α-CGRP [8-37] at doses up to 3 nmol/kg/min was without effect either on resting cardiovascular status, or on the haemodynamic responses to human α-CGRP at 0.03 mg/kg/min (a dose based on our earlier studies (1)). However, human α-CGRP [8-37] at 30 nmol/kg/min caused slight changes in resting cardiovascular status and clearly affected the responses to human α-CGRP (at 0.03 nmol/kg/min), whereas human α-CGRP [8-37] at 300 nmol/kg/min had such marked effects itself (n=2) (see Results) that its influence on the responses to human α-CGRP was impossible to discern reliably. Therefore, in the full experiment , animals (n=8) received human α-CGRP [8-37] at a dose of 30 nmol/kg/min for 20 min. In separate experiments (n=2) the haemodynamic responses to (±)-isoprenaline (0.14 nmol) were assessed before and at the end of the human α-CGRP [8-37] infusion.

At least 3h after human α-CGRP [8-37] infusion the same animals received human α-CGRP at 0.03 nmol/kg/min for 60 min, and during the twentieth to the fortieth min they also received human α-CGRP [8-37] (at 3 nmol/kg/min). This protocol permitted assessment of the responses to human α-CGRP [8-37] alone, human α-CGRP alone, the effect of human α-CGRP [8-37] on the responses to human α-CGRP, and the recovery of the responses to continued infusion of human α-CGRP following cessation of the concurrent infusion of human α-CGRP [8-37]. Infusion of vehicle alone had no consistent cardiovascular effects.

Percentage changes in Doppler shift were taken as an index of changes in flow (8) and percentage changes in vascular conductances were calculated from Doppler shift and mean arterial blood pressure.

Changes relative to baseline were analysed using Friedman's test; $P<0.05$ was taken as significant.

Human α-CGRP and human α-CGRP [8-37] (Celltech Ltd.) were synthesised by standard solid-phase synthetic techniques on an Applied Biosystems 430A using FMOC/tBu chemistry and Rink resin. The peptide was deprotected with trifluoroacetic acid and purified by gel filtration and preparative reverse phase HPLC. Amino acid analysis after acid hydrolysis gave the proper molar ratios. Both peptides were dissolved in isotonic saline containing 1% bovine serum albumin (Sigma) and infused at 0.3 ml/h. (±)-Isoprenaline hydrochloride (Sigma) was dissolved in isotonic saline (1.4 nmol/ml) and given as a bolus dose (100 µl).

RESULTS

Human α-CGRP [8-37] at 30 nmol/kg/min had no effects other than to cause slight reversible reductions in hindquarters flow and vascular conductance (Fig. 1). In addition, infusion of the peptide at this dose had no consistent effects on the haemodynamic responses to isoprenaline (n = 2; Fig. 2).

In the two animals that received human α-CGRP [8-37] at a dose of 300 nmol/kg/min there were substantial tachycardias (maximum +180 and +175 beats/min) preceding increases in mean arterial blood pressure (maximum +12 and +13 mm Hg); these effects were associated with reductions in blood flows (renal, -22 and -34%; mesenteric, -43 and -53%; hindquarters, -47 and -58%) and vascular conductances (renal, -31 and -41%, mesenteric, -49 and -58%; hindquarters, -53 and -62%).

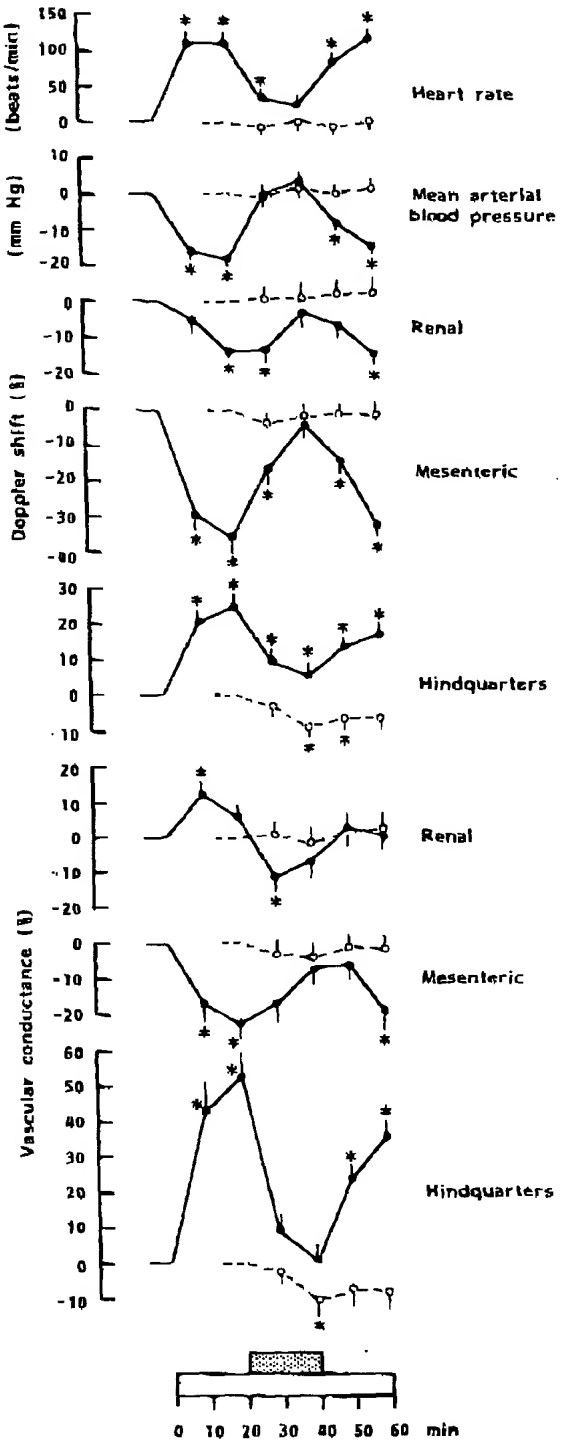

Figure 1. Cardiovascular changes in conscious Long Evans rats (n=8) before, during and after a 20 min infusion of human α-CGRP [8-37] alone at 30 nmol/kg/min (infusion period ▭, changes indicated by O-O). Cardiovascular changes in the same animals during a 60 min infusion (infusion period ▭, changes indicated by ●-●) of human α-CGRP (0.03 nmol/kg/min) with concurrent administration of human α-CGRP [8-37] at 30 nmol/kg/min during the period from 20-40 min (▭). * P<0.05 versus baseline (Friedman's test).

Heart rate (beats/min)

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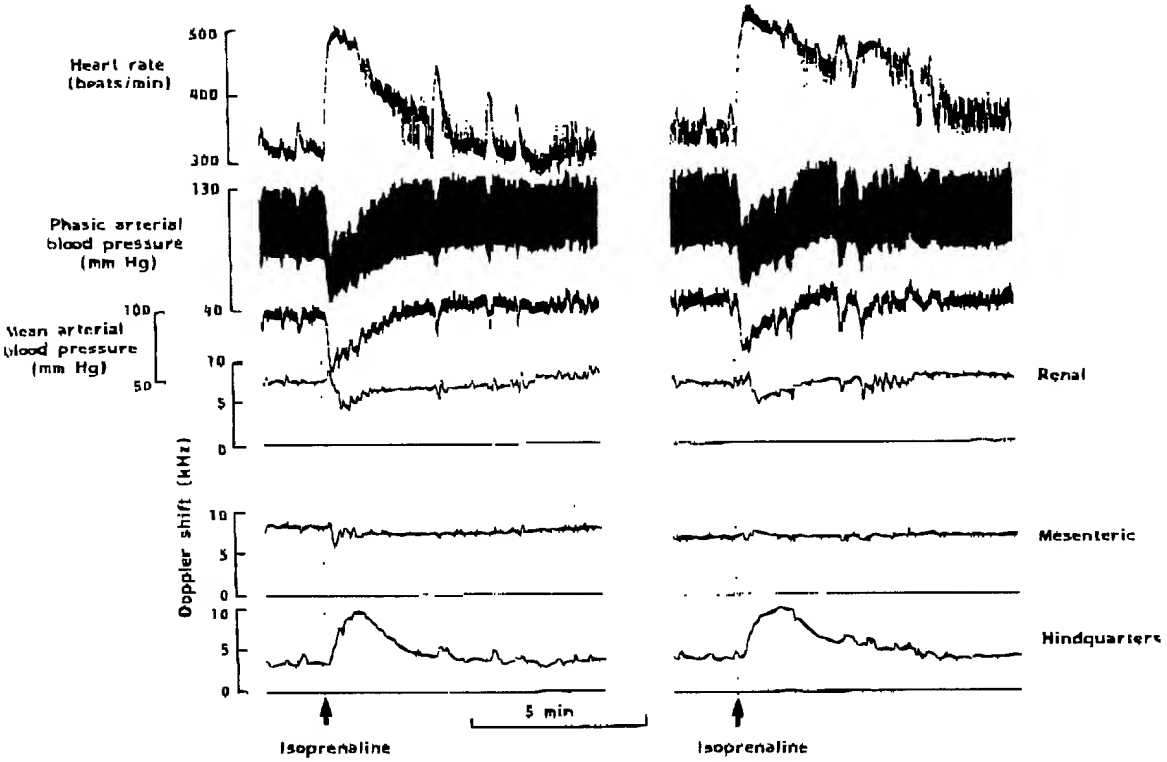

Figure 2. Cardiovascular responses to i.v. bolus doses (0.14 nmol) of (±)-isoprenaline in the same conscious, Long Evans rat under control conditions (left-hand panel) and during the infusion of human α-CGRP [8-37] (30 nmol/kg/min) (right-hand panel).

Infusion of human α-CGRP (0.03 nmol/kg/min) alone caused significant hypotension and tachycardia accompanied by falls in renal and mesenteric flows, but an increase in hindquarters flow (Fig. 1; see (1)). There was a transient renal and sustained hindquarters vasodilatation, but a mesenteric vasoconstriction (Fig. 1). Concurrent administration of human α-CGRP [8-37] (30 nmol/kg/min) abolished the effect of human α-CGRP on all variables, and renal vascular conductance also showed a significant reduction below baseline during the first 10 min of the human α-CGRP [8-37] infusion (Fig. 1). Following cessation of the latter infusion the responses of all variables to the continued infusion of human α-CGRP were re-established, except there was no significant renal vasodilatation (Fig. 1).

DISCUSSION

The present work has shown that human α-CGRP [8-37] (in a dose that has no effects on the cardiovascular actions of isoprenaline) is a reversible antagonist of the haemodynamic effects of human α-CGRP.

The regional haemodynamic responses to infusion of human α-CGRP *in vivo* in conscious rats have been described elsewhere (1) and were

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similar to those described here. We have suggested previously that the marked hindquarters vasodilator response to CGRP and the associated hypotension might trigger activation of baroreflex mechanisms and the renin-angiotensin system, thereby opposing the direct renal and mesenteric vasodilator effects of CGRP (1,9). This proposition is consistent with the present finding that human α-CGRP [8-37] rapidly reversed the hindquarters vasodilator and hypotensive effects of human α-CGRP and then the mesenteric vasoconstriction waned with the hypotension, whereas at the same time there was a renal vasoconstriction (presumably due to unopposed renal vascular effects of angiotensin II (9). Following the cessation of human α-CGRP [8-37] administration, the re-development of the hypotensive and tachycardic effects of human α-CGRP were directly related to the hindquarters vasodilatation, and the secondary nature of the mesenteric vasoconstriction was clearly seen under these conditions, since it followed the hindquarters vasodilatation and accompanying hypotension.

Han et al. (7) recently reported that human α-CGRP [8-37] was a competitive antagonist of the vasodilator effects of human α-CGRP in the isolated, perfused mesenteric vasculature of the rat. Furthermore they found that human α-CGRP [8-37] itself caused vasoconstriction in this preparation through a mechanism other than by acting as an antagonist at calcitonin receptors (5). Han et al. (7) suggested, therefore, that there was a tonic vasodilator effect of endogenous CGRP in the isolated mesenteric vascular bed. In the present work we found that human α-CGRP [8-37] at a dose of 300 nmol/kg/min caused substantial renal, mesenteric and hindquarters vasoconstrictions, together with marked tachycardia and an increase in mean arterial blood pressure. While these findings are consistent with endogenous CGRP being involved in the tonic control of regional vascular conductances in vivo, the occurrence of a substantial tachycardia raises the possibility that these effects were not simply due to human α-CGRP [8-37] acting as an antagonist to endogenous CGRP, since CGRP itself can cause marked increases in heart rate (1). However, the potent vasodilator action of human α-CGRP on the hindquarters vascular bed and the effectiveness of human α-CGRP [8-37] at a dose of 30 nmol/kg/min in antagonizing this response (without changing the hindquarters vasodilator response to isoprenaline) indicates this effect was specific. In addition, it is notable that the hindquarters vascular bed was the only one in which the lower (30 nmol/kg/min) dose of human α-CGRP [8-37] reduced baseline flow and vascular conductance, possibly indicating a more important role for endogenous CGRP in controlling resting haemodynamics in the hindquarters than in the renal or mesenteric vascular beds. However, the effects of human α-CGRP [8-37] alone in the carotid vascular bed, where exogenous human α-CGRP exerts a greater vasodilator effect than in the

hindquarters vascular bed (1), have yet to be studied. Moreover, it will be important to determine if other analogues or fragments of human α-CGRP are more potent antagonists than human α-CGRP [8-37], and what in vivo haemodynamic effects they have in normal and pathophysiological conditions.

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EXHIBIT F

(12) **United States Patent**
Doods et al.

(10) **Patent N .: US 6,521,609 B1**
(45) **Date of Patent: *Feb. 18, 2003**

(54) **USE OF CGRP ANTAGONISTS AND CGRP RELEASE INHIBITORS FOR COMBATING MENOPAUSAL HOT FLUSHES**

(75) Inventors: **Henri Doods**, Warthausen (DE); **Klaus Rudolf**, Warthausen (DE); **Wolfgang Eberlein**, Biberach (DE); **Wolfhard Engel**, Biberach (DE)

(73) Assignee: **Boehringer Ingelheim Pharma KG**, Ingelheim (DE)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **09/614,343**

(22) Filed: **Jul. 12, 2000**

Related U.S. Application Data

(60) Provisional application No. 60/184,800, filed on Feb. 24, 2000.

(30) **Foreign Application Priority Data**

Aug. 10, 1999 (DE) 199 37 304

(51) **Int. Cl.**[7] **A61K 31/454**; A61K 31/55; A61K 31/53; C07D 223/00; C07D 211/00

(52) **U.S. Cl.** **514/183**; 514/212; 514/218; 514/241; 514/247; 514/277; 514/316; 514/331; 540/454; 544/215; 546/184

(58) **Field of Search** 514/183, 212, 514/241, 218, 247, 277, 316, 331

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* cited by examiner

Primary Examiner—Theodore J. Criares
(74) *Attorney, Agent, or Firm*—Robert P. Raymond; Timothy X. Witkowski; Mary-Ellen Devlin

(57) **ABSTRACT**

A method for treating menopausal hot flushes using CGRP antagonists and/or CGRP release inhibitors and the corresponding pharmaceutical compositions containing as active substance one or more CGRP antagonists and/or CGRP release inhibitors, and the preparation thereof.

13 Claims, No Drawings

USE OF CGRP ANTAGONISTS AND CGRP RELEASE INHIBITORS FOR COMBATING MENOPAUSAL HOT FLUSHES

RELATED APPLICATION

This application claims benefit of U.S. Provisional Application No. 60/184,800, filed Feb. 24, 2000.

BACKGROUND OF THE INVENTION

Hot flushes are a common symptom of peri/postmenopausal syndrome the physiology of which is still not fully understood. Apart from hormone replacement therapy, which is a complex intervention and frequently cannot be used long-term owing to its side effects, there has up until now been no simple therapy largely free from side effects for this generally troublesome condition.

Hot flushes are caused by vasodilatation and increased blood flow. A number of publications have mentioned the possibility that CGRP (calcitonin gene-related peptide) plays a part in the occurrence of menopausal hot flushes in oestrogen-deficient women owing to the vasodilatory properties of this neuropeptide ([1]: J. Endocrinol. (1995), 146 (3), 431–437; [2]: Acta Physiol. Scand. (1998), 162(4), 517–522; [3]: Am. J. Obstet. Gynecol. (1996), 175(3, Pt. 1), 638–642). The therapeutic use of CGRP antagonists for treating menopausal syndrome has not previously been proposed in the literature.

It has now been found that the symptoms of menopausal hot flushes can be effectively prevented or their distressing effects substantially alleviated by substances which antagonize the effects of CGRP (CGRP antagonists) or inhibit or reduce the release of CGRP from sensory nerve endings (CGRP release inhibitors), this therapeutic approach being superior to hormone replacement therapy in particular because of its lack of side effects.

SUMMARY OF THE INVENTION

The present invention thus relates to the use of CGRP antagonists and/or CGRP release inhibitors for combating menopausal hot flushes, including both prevention and acute treatment. The use according to the invention preferably comprises monotherapy with a single substance, but also includes combined therapy with a number of substances from the specified groups of active substances. Moreover, the treatment according to the invention may be carried out in addition to conventional hormone replacement therapy.

The invention also relates to the use of CGRP antagonists and/or CGRP release inhibitors for preparing a pharmaceutical composition for treating menopausal hot flushes as well as the corresponding pharmaceutical compositions containing as active substance one or more CGRP antagonists and/or CGRP release inhibitors.

Any pharmaceutically acceptable active substances which antagonize the known effects of CGRP or inhibit the release of CGRP from sensory nerve endings may be used for the purposes of the present invention.

DETAILED DESCRIPTION OF THE INVENTION

Examples of CGRP antagonists include the amino acid derivatives described in WO 98/11128 or DE 199 11 039, as well as the non-peptidic active substances described in WO 98/56779, WO 98/09630, and WO 97/09046.

Examples of CGRP release inhibitors include serotonin 5-HT_{1D}-agonists such as avitriptan, eletriptan, naratriptan,

rizatriptan, sumatriptan or zolmitriptan, as well as 5-HT_{1F}-agonists or NPY-agonists.

Of the CGRP antagonists described in WO 98/11128, the following compounds, for example, may be used for the treatment of menopausal hot flushes, for the preparation of a corresponding pharmaceutical composition and as an ingredient of a corresponding pharmaceutical composition:

(A) 1-[N^2-[3,5-dibromo-N-[[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-L-lysyl]-4-(4-pyridinyl)-piperazine,

(B) 1-[4-amino-3,5-dibromo-N-[[4-(2,3,4,5-tetrahydro-2(1H)-oxo-1,3-benzodiazepin-3-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-piperidinyl)-piperidine,

(C) 1-[N^2-[4-amino-3,5-dibromo-N-[[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-L-lysyl]-4-(4-pyridinyl)-piperazine,

(D) 1-[N^2-[4-amino-3,5-dibromo-N-[[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-L-lysyl]-4-(4-pyridinyl)-piperidine,

(E) 1-[N^2-[3,5-dibromo-N-[[4-(1,3-dihydro-4-phenyl-2(2H)-oxoimidazol-1-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-L-lysyl]-4-(4-pyridinyl)-piperazine,

(F) 1-[N^2-[4-amino-3,5-dibromo-N-[[4-(1,3-dihydro-4-phenyl-2(2H)-oxoimidazol-1-piperidinyl]carbonyl]-D-phenyl-alanyl]-L-lysyl]-4-(4-pyridinyl)-piperazine,

(G) 1-[3,5-dibromo-N-[[4-(3,4-dihydro-2(1H)-oxothieno[3,4-d]pyrimidin-3-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-4-(1-piperidinyl)-piperidine,

(H) 1-[4-amino-3,5-dibromo-N-[[4-(2,4-dihydro-5-phenyl-3(3H)-oxo-1,2,4-triazol-2-yl)-1-piperidinyl]carbonyl]-D-phenyl-alanyl]-4-(1-methyl-4-piperidinyl)-piperidine,

(I) 1-[4-amino-3,5-dibromo-N-[[4-(2,4-dihydro-5-phenyl-3(3H)-oxo-1,2,4-triazol-2-yl)-1-piperidinyl]carbonyl]-D-phenyl-alanyl]-4-(1-piperidinyl)-piperidine,

(J) 1-[4-amino-3,5-dibromo-N-[[4-(2,4-dihydro-5-phenyl-3(3H)-oxo-1,2,4-triazol-2-yl)-1-piperidinyl]carbonyl]-D-phenyl-alanyl]-4-(1-methyl-4-piperidinyl)-piperazine,

(K) 1-[4-amino-3,5-dibromo-N-[[4-(3,4-dihydro-2(1H)-oxothieno[3,2-d]pyrimidin-3-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]4-(1-piperidinyl)-piperidine,

L) 1-[4-amino-3,5-dibromo-N-[[4-[1,3-dihydro-4-[3-(trifluoromethyl)phenyl]-2(2H)-oxoimidazol-1-yl]-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-ethyl-4-piperidinyl)-piperidine,

(M) 1-[4-amino-3,5-dibromo-N-[[4-[3,4-dihydro-2(1H)-oxoquinazolin-3-yl]-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-hexyl-4-piperidinyl)-piperidine,

(N) 1-[4-amino-3,5-dibromo-N-[[4-[3,4-dihydro-2(1H)-oxoquinazolin-3-yl]-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-cyclopropylmethyl-4-piperidinyl)-piperidine,

(O) 1-[N-[[4-[3,4-dihydro-2(1H)-oxoquinazolin-3-yl]-1-piperidinyl]carbonyl]-3-ethenyl-D,L-phenylalanyl]-4-(hexahydro-1H-1-azepinyl)-piperidine,

(P) (R,S)-1-[4-[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]-2-[(4-hydroxy-3,5-dimethylphenyl)methyl]-1,4-dioxobutyl]-4-(1-piperidinyl)-piperidine,

(Q) 1-[4-amino-3,5-dibromo-N-[[4-[N-(aminocarbonyl)-N-phenylamino]-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-piperidinyl)-piperidine,

(R) 1-[4-amino-3,5-dibromo-N-[[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(5-methoxy-4-pyrimidinyl)-piperazine,

(S) 1-[4-amino-3,5-dibromo-N-[[4-(1,1-dioxido-3(4H)-oxo-1,2,4-benzothiadiazin-2-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-piperidinyl)-piperidine,

(T) 1-[4-amino-3,5-dibromo-N-[[4-[2(1H)-oxoquinolin-3-yl]-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-piperidinyl)-piperidine,

(U) 1-[4-amino-3,5-dibromo-N-[[4-[3,4-dihydro-2(1H)-oxoquinazolin-3-yl]-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-[3-(dimethylamino)propyl]-piperazine,

V) 1-[4-amino-3,5-dibromo-N-[[4-[3,4-dihydro-2(1H)-oxoquinazolin-3-yl]-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(4-methyl-1-piperazinyl)-piperidine,

(W) 1-[4-amino-3,5-dibromo-N-[[4-[3,4-dihydro-2(1H)-oxoquinazolin-3-yl]-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-[(1-methyl-4-piperidinyl)carbonyl]-piperazine,

(X) 1-[4-amino-3,5-dibromo-N-[[4-[3,4-dihydro-2(1H)-oxoquinazolin-3-yl]-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-[(1-methyl-4-piperazinyl)carbonyl)-piperazine,

(Y) 1-[4-amino-3,5-dibromo-N-[[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-[4-[4-(dimethylamino)butyl]phenyl]-piperazine,

(Z) 1-[4-amino-3,5-dibromo-N-[[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-[4-(dimethylamino)-1-piperidinyl]-piperidine,

(AA) 1-[N^2-[[4-(1,3-dihydro-4-phenyl-2(2H)-oxoimidazol-1-yl)-1-piperidinyl]carbonyl]-N'-methyl-D-tryptyl]-4-(4-methyl-1-piperazinyl)-piperidine,

(AB) 1-[N^2-[[4-(1,3-dihydro-4-phenyl-2(2H)-oxoimidazol-1-yl)-1-piperidinyl]carbonyl]-N'-(1,1-dimethylethoxycarbonyl)-D-tryptyl]-4-(1-methyl-4-piperidinyl)-piperidine,

(AC) (R,S)-1-[4-[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]-2-[(3,5-dibromo-4-methylphenyl)methyl]-1,4-dioxobutyl]-4-(4-methyl-1-piperazinyl)-piperidine,

(AD) (R,S)-1-[4-[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]-2-[(3,5-dibromo-4-methoxyphenyl)methyl]-1,4-dioxobutyl]-4-(1-methyl-4-piperidinyl)-piperidine,

(AE) (R,S)-1-[4-[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]-2-[(3,4-dibromphenyl)methyl]-1,4-dioxobutyl]-4-(4-methyl-1-piperazinyl)-piperidine,

(AF) 1-[N^2-[N-[[4-(1,3-dihydro-2(2H)-oxobenzimidazol-1-yl)-1-piperidinyl]carbonyl]-3,5-dibromo-D-tyrosyl]-L-lysyl]-4-(4-pyridinyl)-piperazine,

(AG) 1-[4-amino-3,5-dibromo-N-[[4-(1,3-dihydro-6-hydroxy-2(2H)-oxobenzimidazol-1-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-piperidinyl)-piperidine,

(AH) 1-[N^2-[4-amino-3,5-dibromo-N-[[4-(1,3-dihydro-2(2H)-oxobenzimidazol-1-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-$N^{6,N6}$-dimethyl-L-lysyl]-4-(4-pyridinyl)-piperazine,

(AI) 1-[N^2-[4-amino-3,5-dibromo-N-[[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-

phenylalanyl]-$N^{6,N6}$-dimethyl-L-lysyl]-4-(4-pyridinyl)-piperazine,

(AJ) (R,S)-1-[2-(4-amino-3,5-dibromobenzoyl)-4-[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl-)-1-piperidinyl]-4-oxobutyl]-4-(1-piperidinyl)-piperidine,

(AK) 1-[4-amino-3,5-dibromo-N-[[4-(3,4-dihydro-2,2-dioxido-2,1,3-benzothiadiazin-3-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-piperidinyl)-piperidine,

(AL) 1-[4-amino-3,5-dibromo-N-[[4-[1,3-dihydro-2(2H)-oxoimidazo[1,5-c]quinolin-3-yl]-1-piperidinyl]carbonyl]-D-phenyl-alanyl]-4-(1-piperidinyl)carbonyl]-piperidine

(AM) 1-[4-amino-3,5-dibromo-N-[[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-piperidinyl)-piperidine,

(AN) 1-[N^2-[3,5-dibromo-N-[[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-N^6,N^6-dimethyl-L-lysyl]-4-(4-pyridinyl)-piperazine,

(AO) 1-[4-amino-N-[[4-[4-(3-bromophenyl)-1,3-dihydro-2(2H)-oxoimidazol-1-yl]-1-piperidinyl]carbonyl]-3,5-dibromo-D-phenylalanyl]-4-(1-methyl-4-piperidinyl)-piperidine,

(AP) 1-[4-amino-3,5-dibromo-N-[[4-[1,3-dihydro-4-phenyl-2(2H)-oxoimidazol-1-yl]-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(4-methyl-1-piperazinyl)-piperidine,

(AQ) 1-[4-amino-3,5-dibromo-N-[[4-[1,3-dihydro-4-[3-(trifluoromethyl)phenyl]-2-(2H)-oxoimidazol-1-yl]-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-piperidinyl)-piperidine,

(AR) 1-[4-amino-3,5-dibromo-N-[[4-[1,3-dihydro-4-[3-(trifluoromethyl)phenyl]-2(2H)-oxoimidazol-1-yl]-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(exo-8-methyl-8-azabicyclo[3,2,1]oct-3-yl)-piperazine,

(AS) 1-[3,5-dibromo-N-[[4-(1,3-dihydro-4-phenyl-2(2H)-oxoimidazol-1-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-4-(1-piperidinyl)-piperidine,

(AT) 1-[4-amino-3,5-dibromo-N-[[4-[1,3-dihydro-4-[3-(trifluoromethyl)phenyl]-2(2H)-oxoimidazol-1-yl]-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-ethyl-4-piperidinyl)-piperazine,

(AU) 1-[4-amino-3,5-dibromo-N-[[4-[1,3-dihydro-4-phenyl-2(2H)-oxoimidazol-1-yl]-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(hexahydro-4-methyl-1H-1,4-diazepin-1-yl)-piperidine,

(AV) 1-[3,5-dibromo-N-[[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-4-[1-(methylsulfonyl)-4-piperidinyl]-piperidine,

(AW) 1-[4-amino-3,5-dibromo-N-[[4-(1,3-dihydro-4-phenyl-2(2H)-oxoimidazol-1-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-methyl-4-piperidinyl)-piperidine,

(AX) 1-[3,5-dibromo-N-[[4-[1,3-dihydro-4-[3-(trifluoromethyl)phenyl]-2(2H)-oxoimidazol-1-yl]-1-piperidinyl]carbonyl]-D-tyrosyl]-4-(hexahydro-1H-1-azepinyl)-piperidine,

(AY) 1-[3,5-dibromo-N-[[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-4-(1-methyl-4-piperidinyl)-piperidine,

(AZ) 1-[4-amino-3,5-dibromo-N-[[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-

phenylalanyl]-4-(exo-8-methyl-8-azabicyclo[3,2,1]oct-3-yl)-piperazine,

(BA) 1-[4-amino-3,5-dibromo-N-[[4-(1,3-dihydro-4-phenyl-2(2H)-oxoimidazol-1-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-methyl-4-piperidinyl)-piperazine,

(BB) 1-[3,5-dibromo-N-[[4-[1,3-dihydro-4-[3-(trifluoromethyl)phenyl]-2(2H)-oxoimidazol-1-yl]-1-piperidinyl]carbonyl]-D-tyrosyl]-4-(1-piperidinyl)-piperidine,

(BC) 1-[N^6-acetyl-N^2-[3,5-dibromo-N-[[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-L-lysyl]-4-(4-pyridinyl)-piperazine,

(BD) 1-[3,5-dibromo-N-[[4-(1,3-dihydro-4-phenyl-2(2H)-oxoimidazol-1-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-4-(hexahydro-1H-1-azepinyl)-piperidine,

(BE) 1-[4-amino-3,5-dibromo-N-[[4-(1,3-dihydro-4-(3-thienyl)-2(2H)-oxoimidazol-1-yl)-1-piperidinyl]carbonyl]-D-phenyl-alanyl]-4-(1-methyl-4-piperidinyl)-piperidine,

(BF) 1-[4-amino-3,5-dibromo-N-[[4-[1,3-dihydro-4-[3-(trifluoromethyl)phenyl]-2H)-oxoimidazol-1-yl]-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-methyl-4-piperidinyl)-piperidine,

(BG) 1-[3,5-dibromo-N-[[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-4-[1-(hydroxycarbonylmethyl)-4-piperidinyl]-piperidine,

(BH) 1-[4-amino-3,5-dibromo-N-[[4-[3,4-dihydro-2(1H)-oxoquinazolin-3-yl]-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-methylsulphonyl-4-piperidinyl)-piperidine,

(BI) 1-[3,5-dibromo-N-[[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-4-(4-piperidinyl)-piperidine,

(BJ) 1-[4-amino-3,5-dibromo-N-[[4-(1,3-dihydro-4-phenyl-2(2H)-oxoimidazol-1-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-ethyl-4-piperidinyl)-piperidine,

(BK) 1-[4-amino-3,5-dibromo-N-[[4-(1,3-dihydro-4-(3-hydroxyphenyl)-2(2H)-oxoimidazol-1-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-methyl4-piperidinyl)-piperidine,

(BL) 1-[3,5-dibromo-N-[[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-4-(hexahydro-1H-1-azepinyl)-piperidine,

(BM) 1-[4-amino-3,5-dibromo-N-[[4-(1,3-dihydro-4-phenyl-2(2H)-oxoimidazol-1-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-piperidinyl)-piperidine,

(BN) 1-[4-amino-3,5-dibromo-N-[[4-[4-(3-bromophenyl)-1,3-dihydro-2(2H)-oxoimidazol-1-yl]-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(exo-8-methyl-8-azabicyclo[3,2,1]oct-3-yl)-piperazine,

(BO) 1-[4-amino-3,5-dibromo-N-[[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-ethyl-4-piperidinyl)-piperidine,

(BP) 1-[4-amino-3,5-dibromo-N-[[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-ethyl-4-piperidinyl)-piperazine,

(BQ) 1-[4-amino-3,5-dibromo-N-[[4-[1,3-dihydro-4-(3-methoxyphenyl)-2(2H)-oxoimidazol-1-yl]-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(exo-8-methyl-8-azabicyclo[3,2,1]oct-3-yl)-piperazine,

(BR) 1-[3,5-dibromo-N-[[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-4-[1-(cyclopropyl-methyl)-4-piperidinyl]-piperidine,

(BS) 1-[4-amino-3,5-dibromo-N-[[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(hexahydro-1H-1-azepinyl)-piperidine,

(BT) 1-[4-amino-3,5-dibromo-N-[[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(4-piperidinyl)-piperidine,

(BU) 1-[3,5-dibromo-N-[[4-(1,3-dihydro-4-phenyl-2(2H)-oxoimidazol-1-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-4-(4-pyridinyl)-piperidine,

(BV) 1-[3,5-dibromo-N-[[4-[1,3-dihydro-4-[3-(trifluoromethyl)phenyl]-2(2H)-oxoimidazol-1-yl]-1-piperidinyl]carbonyl]-D-tyrosyl]-4-(1-methyl-4-piperidinyl)-piperazine,

(BW) 1-[N^2-[3,5-dibromo-N-[[4-[1,3-dihydro-4-[3-(trifluoromethyl)phenyl]-2(2H)-oxoimidazol-1-yl]-1-piperidinyl]carbonyl]-D-tyrosyl]-L-lysyl]-4-(4-pyridinyl)-piperazine,

(BX) 1-[3,5-dibromo-N-[[4-(1,3-dihydro-4-(3-thienyl)-2(2H)-oxoimidazol-1-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-4-(1-piperidinyl)-piperidine,

(BY) 1-[4-amino-N-[[4-[4-(3-chlorophenyl)-1,3-dihydro-2(2H)-oxoimidazol-1-yl]-1-piperidinyl]carbonyl]-3,5-dibromo-D-phenylalanyl]-4-(1-methyl-4-piperidinyl)-piperidine,

(BZ) 1-[4-amino-3,5-dibromo-N-[[4-[1,3-dihydro-4-[3-(trifluoromethyl)phenyl]-2(2H)-oxoimidazol-1-yl]-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(hexahydro-1H-1-azepinyl)-piperidine,

(CA) 1-[4-amino-3,5-dibromo-N-[[4-[1,3-dihydro-4-[3-(trifluoromethyl)phenyl]-2(2H)-oxoimidazol-1-yl]-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-methyl-4-piperidinyl)-piperazine,

(CB) 1-[4-amino-N-[[4-[4-(3-chlorophenyl)-1,3-dihydro-2(2H)-oxoimidazol 1-yl]-1-piperidinyl]carbonyl]-3,5-dibromo-D-phenylalanyl]-4-(hexahydro-1H-1-azepinyl)-piperidine,

(CC) 1-[4-amino-3,5-dibromo-N-[[4-(1,3-dihydro-4-phenyl-2(2H)-oxoimidazol-1-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(4-pyridinyl)-piperazine,

(CD) 1-[3,5-dibromo-N-[[4-(1,3-dihydro-4-phenyl-2(2H)-oxoimidazol-1-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-4-(1-methyl-4-piperidinyl)-piperidine,

(CE) 1-[4-amino-3,5-dibromo-N-[[4-[1,3-dihydro-4-phenyl-2(2H)-oxoimidazol-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-[4-(1-oxoethyl)phenyl]-piperazine,

(CF) 1-[3,5-dibromo-N-[[4-[3,4-dihydro-2(1H)-oxoquinazolin-3-yl]-1-piperidinyl]carbonyl]-D-tyrosyl]-4-(1-methyl-4-piperidinyl)-piperazine,

(CG) 1-[4-amino-3,5-dibromo-N-[[4-[1,3-dihydro-4-(3-nitrophenyl)-2(2H)-oxoimidazol-1-yl]-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-methyl-4-piperidinyl)-piperidine,

(CH) 1-[4-amino-3,5-dibromo-N-[[4-[3,4-dihydro-2(1H)-oxoquinazolin-3-yl]-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-pyrrolidinyl)-piperidine,

(CI) 1-[4-amino-3,5-dibromo-N-[[4-(1,3-dihydro-4-phenyl-2(2H)-oxoimidazol-1-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(hexahydro-1H-1-azepinyl)-piperidine and

(CJ) 1-[4-amino-3,5-dibromo-N-[[4-(1,3-dihydro-4-(3-thienyl)-2(2H)-oxoimidazol-1-yl)-1-piperidinyl]carbonyl]-D-phenyl-alanyl]-4-(1-methyl-4-piperidinyl)-piperazine,

the tautomers, the diastereomers, the enantiomers, the mixtures thereof and the physiologically acceptable salts thereof.

The following compounds are preffered:

(A) 1-[N²-[3,5-dibromo-N-[[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-L-lysyl]-4-(4-pyridinyl)-piperazine,

(B) 1-[4-amino-3,5-dibromo-N-[[4-(2,3,4,5-tetrahydro-2(1H)-oxo-1,3-benzodiazepin-3-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-piperidinyl)-piperidine,

(I) 1-[4-amino-3,5-dibromo-N-[[4-(2,4-dihydro-5-phenyl-3(3H)-oxo-1,2,4-triazol-2-yl)-1-piperidinyl]carbonyl]-D-phenyl-alanyl]-4-(1-piperidinyl)-piperidine,

(J) 1-[4-amino-3,5-dibromo-N-[[4-(2,4-dihydro-5-phenyl-3(3H)-oxo-1,2,4-triazol-2-yl)-1-piperidinyl]carbonyl]-D-phenyl-alanyl]-4-(1-methyl-4-piperidinyl)-piperazine,

(AC) (R,S)-1-[4-[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]-2-[(3,5-dibromo-4-methylphenyl)methyl]-1,4-dioxobutyl]-4-(4-methyl-1-piperazinyl)-piperidine,

(AF) 1-[N²-[N-[[4-(1,3-dihydro-2(2H)-oxobenzimidazol-1-yl)-1-piperidinyl]carbonyl]-3,5-dibromo-D-tyrosyl]-L-lysyl]-4-(4-pyridinyl)-piperazine, and

(AM) 1-[4-amino-3,5-dibromo-N-[[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-piperidinyl)-piperidine,

the tautomers, the diastereomers, the enantiomers, the mixtures thereof and the physiologically acceptable salts thereof.

The following compounds are particularly preferred:

(A) 1-[N²-[3,5-dibromo-N-[[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-L-lysyl]-4-(4-pyridinyl)-piperazine; and

(B) 1-[4-amino-3,5-dibromo-N-[[4-(2,3,4,5-tetrahydro-2(1H)-oxo-1,3-benzodiazepin-3-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-piperidinyl)-piperidine,

the tautomers, the diastereomers, the enantiomers, the mixtures thereof and the physiologically acceptable salts thereof.

The dosage required to produce the desired effect is appropriately 0.0001 to 3 mg/kg of body weight, preferably 0.01 to 1 mg/kg of body weight for intravenous or subcutaneous administration and 0.01 to 10 mg/kg of body weight, preferably 0.1 to 10 mg/kg of body weight for administration by oral or nasal route or by inhalation, 1 to 3 times a day in each case.

If the treatment with CGRP antagonists and/or CGRP release inhibitors is given as a supplement to conventional hormone replacement therapy, it is advisable to reduce the doses given above, and in this case the dosage may range from 1/5 of the lower limits specified above up to 1/1 of the upper limits specified above.

For this purpose, the CGRP antagonists and/or CGRP release inhibitors may be formulated with one or more conventional inert carriers and/or diluents, e.g., with corn starch, lactose, glucose, microcrystalline cellulose, magnesium stearate, polyvinylpyrrolidone, citric acid, tartaric acid, water, water/ethanol, water/glycerol, water/sorbitol, water/polyethyleneglycol, propylene glycol, cetylstearyl alcohol, carboxymethylcellulose or fatty substances such as hard fat or suitable mixtures thereof in conventional galenic preparations such as plain or coated tablets, capsules, powders, suspensions, solutions, metering aerosols or suppositories.

Preparations which are particularly suitable for treating menopausal hot flushes are those which contain one of the active substances:

(A) 1-[N²-[3,5-dibromo-N-[[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-L-lysyl]-4-(4-pyridinyl)-piperazine,

(B) 1-[4-amino-3,5-dibromo-N-[[4-(2,3,4,5-tetrahydro-2(1H)-oxo-1,3-benzodiazepin-3-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-piperidinyl)-piperidine,

(I) 1-[4-amino-3,5-dibromo-N-[[4-(2,4-dihydro-5-phenyl-3(3H)-oxo-1,2,4-triazol-2-yl)-1-piperidinyl]carbonyl]-D-phenyl-alanyl]-4-(1-piperidinyl)-piperidine,

(J) 1-[4-amino-3,5-dibromo-N-[[4-(2,4-dihydro-5-phenyl-3(3H)-oxo-1,2,4-triazol-2-yl)-1-piperidinyl]carbonyl]-D-phenyl-alanyl-4-(1-methyl-4-piperidinyl)-piperazine,

(AC) (R,S)-1-[4-[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]-2-[(3,5-dibromo-4-methylphenyl)methyl]-1,4-dioxobutyl]-4-(4-methyl-1-piperazinyl)-piperidine,

(AF) 1-[N²-[N-[[4-(1,3-dihydro-2(2H)-oxobenzimidazol-1-yl)-1-piperidinyl]carbonyl]-3,5-dibromo-D-tyrosyl]-L-lysyl]-4-(4-pyridinyl)-piperazine, or

(AM) 1-[4-amino-3,5-dibromo-N-[[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-piperidinyl)-piperidine,

in one of the following pharmaceutical formulations:

capsules for powder inhalation containing 1 mg of active substance, preferably active substance (A) or (B),

inhalable solution for nebulisers containing 1 mg of active substance, preferably active substance (A) or (B),

propellant gas-operated metering aerosol containing 1 mg of active substance, preferably active substance (A) or (B),

nasal spray containing 1 mg of active substance, preferably active substance (A) or (B),

tablets containing 20 mg of active substance, preferably active substance (B),

capsules containing 20 mg of active substance, preferably active substance (B),

aqueous solution for nasal application containing 10 mg of active substance, preferably active substance (A) or (B),

aqueous solution for nasal application containing 5 mg of active substance, preferably active substance (A) or (B), or

suspension for nasal application containing 20 mg of active substance, preferably active substance (A) or (B).

CGRP is released by sensory nerves, e.g., the trigeminal nerve which innervates part of the skin of the face. It has already been shown that stimulation of the trigeminal gan-

glion in humans leads to an increase in the CGRP plasma level and causes reddening of the face ([1]: P. J. Goadsby et al., Annals of Neurology, Vol. 23, No. 2,1988, 193–196,).

To demonstrate that hot flushes can be successfully treated using CGRP antagonists and CGRP release inhibitors, an increased release of endogenous CGRP was induced in marmosets by stimulating the trigeminal ganglion, leading to increased blood flow through the blood vessels of the skin. The efficacy of the following test substances was characterised by determining the dose administered i.v. which reduces by 50% the increased blood flow through the skin of the face which has been brought about by endogenous CGRP:

(A) is 1-[N^2-[3,5-dibromo-N-[[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-L-lysyl]-4-(4-pyridinyl)-piperazine,

(B) is 1-[4-amino-3,5-dibromo-N-[[4-(2,3,4,5-tetrahydro-2(M11)-oxo-1,3-benzodiazepin-3-yl)-1-piperidinyl] carbonyl]-D-phenylalanyl]-4-(1-piperidinyl)-piperidine,

(AC) is (R,S)-1-[4-[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]-2-[(3,5-dibromo-4-methylphenyl) methyl]-1,4-dioxobutyl]-4-(4-methyl-1-piperazinyl)-piperidine,

(AM) is 1-[4-amino-3,5-dibromo-N-[[4-(3,4-dihydro-2 (1H)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-piperidinyl)-piperidine,

(DA) is sumatriptan, and

(DB) is zolmitriptan.

Description of the Method

Marmosets of both sexes (300–400 g) are anaesthetized with pentobarbital (initially with 30 mg/kg, i.p., followed by infusion of 6 mg/kg/h, i.m.). The body temperature is maintained at 37° C. using a heating plate. Pancuronium is administered as a muscle relaxant (initially 1 mg/kg, 0.5 mg after each hour thereafter). The animal's head is secured in a stereotactical apparatus. After the skin on the head has been opened using a lengthwise incision, a small hole is drilled in the skull and a bipolar electrode (Rhodes SNES 100) is lowered into the trigeminal ganglion. Locating the ganglion is made easier by the use of an X-ray which shows up the bone structure of the skull. The petrous bone serves as a guide for placing the electrode (CCX-Digital X-ray apparatus). The position of the electrode in the ganglion is monitored at the end of each experiment. The stimulation parameters are: 10 Hz, 2 mA, 2 msec, for 30 seconds. The blood flow in the micro-vessels of the facial skin is determined by laser Doppler flow measurement using a PeriFlux Laser Doppler System. The animals are exposed to 2 to 3 stimulation periods at intervals of 30 minutes in each case. The first stimulation serves as a reference value for the other stimulations. The test substances are administered i.v. 5 minutes before the 2nd and 3rd stimulation periods.

TABLE 1

Substance	50% dose
A	0.003 mg/kg
B	0.042 mg/kg
AC	0.018 mg/kg
AM	0.046 mg/kg
DA	0.280 mg/kg
DB	0.035 mg/kg

TABLE 1-continued

Substance	50% dose

"50% dose" is an i.v. dose which reduces by 50% the increased blood flow through the facial skin caused by endogenous CGRP

The Examples which follow describe pharmaceutical preparations which contain as active substance a CGRP antagonist or CGRP release inhibitor for use according to the invention, preferably one of the amino acid derivatives described in WO 98/11128 or DE 199 11 039, for example one of the abovementioned active substances (A) or (B):

EXAMPLE I

Capsules for Powder Inhalation with 1 mg of Active Substance (A) or (B)

Composition:

1 capsule for powder inhalation contains:

active substance (A) or (B)	1.0 mg
lactose	20.0 mg
hard gelatine capsules	50.0 mg
	71.0 mg

Method of Preparation

The active substance is ground to the particle size needed for inhalation. The ground active substance is homogeneously mixed with the lactose. The mixture is packed into hard gelatine capsules.

EXAMPLE II

Inhalable Solution for Respimat® with 1 mg of Active Substance (A) or (B)

Composition:

1 spray contains:

active substance (A) or (B)	1.0 mg
benzalkonium chloride	0.002 mg
disodium edetate	0.0075 mg
purified water	ad 15.0 µl

Method of Preparation

The active substance and benzalkonium chloride are dissolved in water and packed in Respimate® cartridges.

EXAMPLE III

Inhalable Solution for Nebulisers with 1 mg of Active Substance (A) or (B)

Composition: 1 vial contains:

active substance (A) or (B)	0.1 g
sodium chloride	0.18 g
benzalkonium chloride	0.002 g
purified water	ad 20.0 ml

Method of Preparation

Active substance, sodium chloride and benzalkonium chloride are dissolved in water.

EXAMPLE IV

Propellant Gas-operated Metering Aerosol with 1 mg of Active Substance (A) or (B)

Composition:

1 spray contains:

active substance (A) or (B)	1.0 mg
lecithin	0.1 %
propellant gas	ad 50.0 µl

Method of Preparation

The micronised active substance is homogeneously suspended in the mixture of lecithin and propellant gas. The suspension is transferred into a pressurised container with a metering valve.

EXAMPLE V

Nasal Spray with 1 mg of Active Substance (A) or (B)

Composition:

1 spray jet contains

active substance (A) or (B)	1.0 mg
mannitol	5.0 mg
disodium edetate	0.05 mg
ascorbic acid	1.0 mg
purified water	ad 0.1 ml

Method of Preparation

The active substance and the excipients are dissolved in water and transferred into a suitable container.

EXAMPLE VI

Injectable Solution with 5 mg of Active Substance (A) or (B) per 5 ml

Composition:

active substance (A) or (B) in basic form	5 mg
acid/salt-forming agent in the amount needed to form a neutral salt	q.s.
glucose	250 mg
human serum albumin	10 mg
glycofurol	250 mg
water for injections	ad 5 ml

Method of Preparation

Dissolve the glycofurol and glucose in water for injections (Wfl); add human serum albumin; add salt-forming agent; dissolve active substance with heating; make up to specified volume with Wfl; transfer into ampoules under nitrogen gas.

EXAMPLE VII

Injectable Solution for Subcutaneous Administration Containing 5 mg of Active Substance (A) or (B) per 1 ml

Composition:

active substance (A) or (B)	5 mg
glucose	50 mg
polysorbate 80 (Tween 80)	2 mg
water for injections	ad 1 ml

Method of Preparation

Dissolve glucose and polysorbate in water for injections; dissolve active substance with heating or using ultrasound; make up to specified volume with Wfl; transfer into ampoules under inert gas.

EXAMPLE VIII

Injectable Solution Containing 100 mg of Active Substance (A) or (B) per 10 ml

Composition:

active substance (A) or (B)	100 mg
monopotassium dihydrogen phosphate (KH_2PO_4)	12 mg
disodium hydrogen phosphate ($Na_2HPO_4 \cdot 2H_2O$)	2 mg
sodium chloride	180 mg
human serum albumin	50 mg
polysorbate 80	20 mg
water for injections	ad 10 ml

Method of Preparation

Dissolve polysorbate 80, sodium chloride, monopotassium dihydrogen phosphate, and disodium hydrogen phosphate in water for injections (Wfl); add human serum albumin; dissolve active substance with heating; make up to specified volume with Wfl; transfer into ampoules.

EXAMPLE IX

Lyophilisate Containing 10 mg of Active Substance (A) or (B)

Composition:

active substance (A) or (B) in basic form	10 mg
acid/salt-forming agent in the amount needed to form a neutral salt	q.s.
mannitol	300 mg
water for injections	ad 2 ml

Method of Preparation

Dissolve mannitol in water for injections (Wfl); add salt-forming agent; dissolve active substance with heating; make up to specified volume with Wfl; transfer into vials; freeze-dry.

Solvent for Lyophilisate

polysorbate 80 (Tween 80)	20 mg
mannitol	200 mg
water for injections	ad 10 ml

Method of Preparation

Dissolve polysorbate 80 and mannitol in water for injections (WFI); transfer into ampoules.

EXAMPLE X

Lyophilisate Containing 5 mg of Active Substance (A) or (B)

Composition:

active substance (A) or (B) in basic form	5 mg
polar or nonpolar solvent (which can be removed by freeze drying)	ad 2 ml

Method of Preparation

Dissolve active substance in suitable solvent; transfer into vials; freeze-dry.

Solvent for Lyophilisate

polysorbate 80 (Tween 80)	5 mg
mannitol	100 mg
water for injections	ad 2 ml

Method of Preparation

Dissolve polysorbate 80 and mannitol in water for injections (WFI); transfer into ampoules.

EXAMPLE XI

Tablets Containing 20 mg of Active Substance (A) or (B)

Composition:

active substance (A) or (B)	20 mg
lactose	120 mg
maize starch	40 mg
magnesium stearate	2 mg
Povidone K 25	18 mg

Method of Preparation

Homogeneously mix the active substance, lactose and maize starch; granulate with an aqueous solution of Povidone; mix with magnesium stearate; press in a tablet press; weight of tablet 200 mg.

EXAMPLE XII

Capsules Containing 20 mg of Active Substance (A) or (B)

Composition:

active substance (A) or (B)	20 mg
maize starch	80 mg
highly dispersed silica	5 mg
magnesium stearate	2.5 mg

Method of Preparation

Homogeneously mix the active substance, maize starch and silica; mix with magnesium stearate; transfer mixture into size 3 hard gelatine capsules in a capsule filling machine.

EXAMPLE XIII

Suppositories Containing 50 mg of Active Substance (A) or (B)

Composition:

active substance (A) or (B)	50 mg
hard fat (Adeps solidus)	q.s. ad 1700 mg

Method of Preparation

Melt the hard fat at about 38° C.; homogeneously disperse the ground active substance in the molten hard fat; after cooling to about 35° C., pour into chilled molds.

EXAMPLE XIV

Aqueous Solution for Nasal Administration Containing 10 mg of Active Substance (A) or (B)

Composition:

active substance (A) or (B)	10.0 mg
hydrochloric acid in the amount needed to form a neutral salt	
methyl parahydroxybenzoate (PHB)	0.01 mg
propyl parahydroxybenzoate (PHB)	0.005 mg
purified water	ad 1.0 ml

Method of Preparation

The active substance is dissolved in purified water; hydrochloric acid is added until the solution is clear; methyl and propyl PHB are added; the solution is made up to the specified volume with purified water; the solution is filtered sterile and transferred into a suitable container.

EXAMPLE XV

Aqueous Solution for Nasal Administration Containing 5 mg of Active Substance (A) or (B)

Composition:

active substance (A) or (B)	5 mg
1,2-propanediol	300 mg
hydroxyethylcellulose	5 mg
sorbic acid	1 mg
purified water	ad 1 ml

Method of Preparation

The active substance is dissolved in 1,2-propanediol; a hydroxyethyl-cellulose solution in purified water containing sorbic acid is prepared and added to the solution of active substance; the solution is filtered sterile and transferred into a suitable container.

EXAMPLE XVI

Aqueous Solution for Intravenous Administration Containing 5 mg of Active Substance (A or (B)

Composition:

active substance (A) or (B)	5 mg
1,2-propanediol	300 mg
mannitol	50 mg
water for injections (Wfi)	ad 1 ml

Method of Preparation

The active substance is dissolved in 1,2-propanediol; the solution is made up to approximately the specified volume with Wfi; the mannitol is added and made up to approximately the specified volume with Wfi; the solution is filtered sterile, transferred into individual containers and autoclaved.

EXAMPLE XVII

Liposomal Formulation for Intravenous Injection Containing 7.5 . mg of Active Substance (A) or (B)

Composition:

active substance (A) or (B)	7.5 mg
egg lecithin, e.g., Lipoid E 80	100.0 mg
cholesterol	50.0 mg
glycerol	50.0 mg
water for injections	ad 1.0 ml

Method of Preparation

The active substance is dissolved in a mixture of lecithin and cholesterol; the solution is added to a mixture of glycerol and Wfi and homogenized by high pressure homogenization or by the Microfluidizer technique; the liposomal formulation obtained is transferred into a suitable container under aseptic conditions.

EXAMPLE XVIII

Suspension for Nasal Administration Containing 20 mg of Active Substance (A) or (B)

Composition:

active substance (A) or (B)	20.0 mg
carboxymethylcellulose (CMC)	20.0 mg
sodium monohydrogen phosphate/sodium dihydrogen phosphate buffer pH 6.8	q.s.
sodium chloride	8.0 mg
methyl parahydroxybenzoate	0.01 mg
propyl parahydroxybenzoate	0.003 mg
purified water	ad 1.0 ml

Method of Preparation

The active substance is suspended in an aqueous CMC solution; the other ingredients are added successively to the suspension and the suspension is topped up to the specified volume with purified water.

EXAMPLE XIX

Aqueous Solution for Subcutaneous Administration with 10 mg of Active Substance (A) or (B)

Composition:

active substance (A) or (B)	10.0 mg
sodium monohydrogen phosphate/sodium dihydrogen phosphate buffer	q.s. ad pH 7.0
sodium chloride	4.0 mg
water for injections	ad 0.5 ml

Method of Preparation

The active substance is dissolved in the phosphate buffer solution, after the addition of the common salt the solution is made up to the specified volume with water. The solution is filtered sterile, transferred into a suitable container and autoclaved.

EXAMPLE XX

Aqueous Suspension for Subcutaneous Administration Containing 5 mg of Active Substance (A) or (B)

Composition:

active substance (A) or (B)	5.0 mg
polysorbate 80	0.5 mg
water for injections	0.5 ml

Method of Preparation

The active substance is suspended in the polysorbate 80 solution and comminuted to a particle size of about 1 μm using a suitable dispersing technique (e.g., wet grinding, high pressure homogenization, microfluidization, etc.). The suspension is transferred into a corresponding container under aseptic conditions.

We claim:

1. A method for treating menopausal hot flushes, comprising administering to a host in need of such treatment an

active substance selected from the group consisting of CGRP antagonists and CGRP release inhibitors.

2. The method according to claim 1, wherein the method is effected as a monotherapy with a single active substance.

3. The method according to claim 1, wherein the method is effected as a supplement to hormone replacement therapy.

4. The method according to claim 1, wherein the active substance is a CGRP antagonist.

5. The method according to claim 4, wherein the CGRP antagonist is selected from the group consisting of:

(A) 1-[N^2-[3,5-dibromo-N-[[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-L-lysyl]-4-(4-pyridinyl)-piperazine;

(B) 1-[4-amino-3,5-dibromo-N-[[4-(2,3,4,5-tetrahydro-2(1H)-oxo-1,3-benzodiazepin-3-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-piperidinyl)-piperidine;

(C) 1-[N^2-[4-amino-3,5-dibromo-N-[[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-L-lysyl]-4-(4-pyridinyl)-piperazine;

(D) 1-[N^2-[4-amino-3,5-dibromo-N-[[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-L-lysyl]-4-(4-pyridinyl)-piperidine;

(E) 1-[N^2-[3,5-dibromo-N-[[4-(1,3-dihydro-4-phenyl-2(2H)-oxoimidazol-1-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-L-lysyl]-4-(4-pyridinyl)-piperazine;

(F) 1-[N^2-[4-amino-3,5-dibromo-N-[[4-(1,3-dihydro-4-phenyl-2(2H)-oxoimidazol-1-yl-1-piperidinyl]carbonyl]-D-phenyl-alanyl]-L-lysyl]-4-(4-pyridinyl)-piperazine;

(G) 1-[3,5-dibromo-N-[[4-(3,4-dihydro-2(1H)-oxothieno[3,4-d]pyrimidin-3-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-4-(1-piperidinyl)-piperidine;

(H) 1-[4-amino-3,5-dibromo-N-[[4-(2,4-dihydro-5-phenyl-3(3H)-oxo-1,2,4-triazol-2-yl)-1-piperidinyl]carbonyl]-D-phenyl-alanyl]-4-(1-methyl-4-piperidinyl)-piperidine;

(I) 1-[4-amino-3,5-dibromo-N-[[4-(2,4-dihydro-5-phenyl-3(3H)-oxo-1,2,4-triazol-2-yl)-1-piperidinyl]carbonyl]-D-phenyl-alanyl]-4-(1-piperidinyl)-piperidine;

(J) 1-[4-amino-3,5-dibromo-N-[[4-(2,4-dihydro-5-phenyl-3(3H)-oxo-1,2,4-triazol-2-yl)-1-piperidinyl]carbonyl]-D-phenyl-alanyl]-4-(1-methyl-4-piperidinyl)-piperazine;

(K) 1-[4-amino-3,5-dibromo-N-[[4-(3,4-dihydro-2(1H)-oxothieno[3,2-d]pyrimidin-3-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-piperidinyl)-piperidine;

(L) 1-[4-amino-3,5-dibromo-N-[[4-[1,3-dihydro-4-[3-(tri-fluoromethyl)phenyl]-2(2H)-oxoimidazol-1-yl]-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-ethyl-4-piperidinyl)-piperidine;

(M) 1-[4-amino-3,5-dibromo-N-[[4-[3,4-dihydro-2(1H)-oxoquinazolin-3-yl]-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-hexyl-4-piperidinyl)-piperidine;

(N) 1-[4-amino-3,5-dibromo-N-[[4-[3,4-dihydro-2(1H)-oxoquinazolin-3-yl]-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-cyclopropylmethyl-4-piperidinyl)-piperidine;

(O) 1-[N-[[4-[3,4-dihydro-2(1H)-oxoquinazolin-3-yl]-1-piperidinyl]carbonyl]-3-ethenyl-D,L-phenylalanyl]-4-(hexahydro-1H-1-azepinyl)-piperidine;

(P) (R,S)-1-[4-[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]-2-[(4-hydroxy-3,5-dimethylphenyl)methyl]-1,4-dioxobutyl]-4-(1-piperidinyl)-piperidine;

(Q) 1-[4-amino-3,5-dibromo-N-[[4-[N-(aminocarbonyl)-N-phenylamino]-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-piperidinyl)-piperidine;

(R) 1-[4-amino-3,5-dibromo-N-[[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(5-methoxy-4-pyrimidinyl)-piperazine;

(S) 1-[4-amino-3,5-dibromo-N-[[4-(1,1-dioxido-3(4H)-oxo-1,2,4-benzothiadiazin-2-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-piperidinyl)-piperidine;

(T) 1-[4-amino-3,5-dibromo-N-[[4-[2(1H)-oxoquinolin-3-yl]-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-piperidinyl)-piperidine;

(U) 1-[4-amino-3,5-dibromo-N-[[4-[3,4-dihydro-2(1H)-oxoquinazolin-3-yl]1-piperidinyl]carbonyl]-D-phenylalanyl]-4-[3-(dimethylamino)propyl]-piperazine;

(V) 1-[4-amino-3,5-dibromo-N-[[4-[3,4-dihydro-2(1H)-oxoquinazolin-3-yl]-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(4-methyl-1-piperazinyl)-piperidine;

(W) 1-[4-amino-3,5-dibromo-N-[[4-[3,4-dihydro-2(1H)-oxoquinazolin-3-yl]-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-[(1-methyl-4-piperidinyl)carbonyl]-piperazine;

(X) 1-[4-amino-3,5-dibromo-N-[[4-[3,4-dihydro-2(1H)-oxoquinazolin-3-yl]-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-[(1-methyl-4-piperazinyl)carbonyl]-piperazine;

(Y) 1-[4-amino-3,5-dibromo-N-[[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-[4-[4-(dimethylamino)butyl]phenyl]-piperazine;

(Z) 1-[4-amino-3,5-dibromo-N-[[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-[4-(dimethylamino)-1-piperidinyl]-piperidine;

(AA) 1-[N^2-[[4-(1,3-dihydro-4-phenyl-2(2H)-oxoimidazol-1-yl)-1-piperidinyl]carbonyl]-N'-methyl-D-tryptyl]-4-(4-methyl-1-piperazinyl)-piperidine;

(AB) 1-[N^2-[[4-(1,3-dihydro-4-phenyl-2(2H)-oxoimidazol-1-yl)-1-piperidinyl]carbonyl]-N'-(1,1-dimethylethoxycarbonyl)-D-tryptyl]-4-(1-methyl-4-piperidinyl)-piperidine;

(AC) (R,S)-1-[4-[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]-2-[(3,5-dibromo-4-methylphenyl)methyl]-1,4-dioxobutyl]-4-(4-methyl-1-piperazinyl)-piperidine;

(AD) (R,S)-1-[4-[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]-2-[(3,5-dibromo-4-methoxyphenyl)methyl]-1,4-dioxobutyl]-4-(1-methyl-4-piperidinyl)-piperidine;

(AE) (R,S)-1-[4-[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]-2-[(3,4-dibromophenyl)methyl]-1,4-dioxobutyl]-4-(4-methyl-1-piperazinyl)-piperidine;

(AF) 1-[N -[N-[[4-(1,3-dihydro-2(2H)-oxobenzimidazol-1-yl)-1-piperidinyl]carbonyl]-3,5-dibromo-D-tyrosyl]-L-lysyl]-4-(4-pyridinyl)-piperazine;

(AG) 1-[4-amino-3,5-dibromo-N-[[4-(1,3-dihydro-6-hydroxy-2(2H)-oxobenzimidazol-1-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-piperidinyl)-piperidine;

(AH) 1-[N^2-[4-amino-3,5-dibromo-N-[[4-(1,3-dihydro-2(2H)-oxobenzimidazol-1-yl)-1-piperidinyl]carbonyl]-

D-phenylalanyl]-N^6,N^6-dimethyl-L-lysyl]-4-(4-pyridinyl)-piperazine;

(AI) 1-[N^2-[4-amino-3,5-dibromo-N-[[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-N^6,N^6-dimethyl-L-lysyl]-4-(4-pyridinyl)-piperazine;

(AJ) (R,S)-1-[2-(4-amino-3,5-dibromobenzoyl)-4-[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]-4-oxobutyl]-4-(-piperidinyl)-piperidine;

(AK) 1-[4-amino-3,5-dibromo-N-[[4-(3,4-dihydro-2,2-dioxido-2,1,3-benzothiadiazin-3-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-piperidinyl)-piperidine;

(AL) 1-[4-amino-3,5-dibromo-N-[[4-[1,3-dihydro-2(2H)-oxoimidazo[4,5-c]quinolin-3-yl]-1-piperidinyl]carbonyl]-D-phenyl-alanyl]-4-(1-piperidinyl)carbonyl]-piperidine;

(AM) 1-[4-amino-3,5-dibromo-N-[[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-piperidinyl)-piperidine;

(AN) 1-[N^2-[3,5-dibromo-N-[[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-N^6,N^6-dimethyl-L-lysyl]-4-(4-pyridinyl)-piperazine ;

(AO) 1-[4-amino-N-[[4-[4-(3-bromophenyl)-1,3-dihydro-2(2H)-oxoimidazol-1-yl]-1-piperidinyl]carbonyl]-3,5-dibromo-D-phenylalanyl]-4-(1-methyl-4-piperidinyl)-piperidine;

(AP) 1-[4-amino-3,5-dibromo-N-[[4-[1,3-dihydro-4-phenyl-2(2H)-oxoimidazol-1-yl]-piperidinyl]carbonyl]-D-phenylalanyl]-4-(4-methyl-1-piperazinyl)-piperidine;

(AQ) 1-[4-amino-3,5-dibromo-N-[[4-[1,3-dihydro-4-[3-(trifluoromethyl)phenyl]-2(2H)-oxoimidazol-1-yl]-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-piperidinyl)-piperidine;

(AR) 1-[4-amino-3,5-dibromo-N-[[4-[1,3-dihydro-4-[3-(trifluoromethyl)phenyl]-2(2H)-oxoimidazol-1-yl]-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(exo-8-methyl-8-azabicyclo[3,2,1]oct-3-yl)-piperazine;

(AS) 1-[3,5-dibromo-N-[[4-(1,3-dihydro-4-phenyl-2(2H)-oxoimidazol-1-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-4-(1-piperidinyl)-piperidine;

(AT) 1-[4-amino-3,5-dibromo-N-[[4-[1,3-dihydro-4-[3-(trifluoromethyl)phenyl]-2(2H)-oxoimidazol-1-yl]-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-ethyl-4-piperidinyl)-piperazine;

(AU) 1-[4-amino-3,5-dibromo-N-[[4-[1,3-dihydro-4-phenyl-2(2H)-oxoimidazol-1-yl]-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(hexahydro-4-methyl-1H-1,4-diazepin-1-yl)piperidine;

(AV) 1-[3,5-dibromo-N-[[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-4-[1-(methylsulfonyl)-4-piperidinyl]-piperidine;

(AW) 1-[4-amino-3,5-dibromo-N-[[4-(1,3-dihydro-4-phenyl-2(2H)-oxoimidazol-1-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-methyl-4-piperidinyl)-piperidine;

(AX) 1-[3,5-dibromo-N-[[4-[1,3-dihydro-4-[3-(trifluoromethyl)phenyl]-2(2H)-oxoimidazol-1-yl]-1-piperidinyl]carbonyl]-D-tyrosyl]-4-(hexahydro-1H-1-azepinyl)-piperidine;

(AY) 1-[3,5-dibromo-N-[[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-4-(1-methyl-4-piperidinyl)-piperidine;

(AZ) 1-[4-amino-3,5-dibromo-N-[[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(exo-8-methyl-8-azabicyclo[3,2,1]oct-3-yl)-piperazine;

(BA) 1-[4-amino-3,5-dibromo-N-[[4-(1,3-dihydro-4-phenyl-2(2H)-oxoimidazol-1-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-methyl-4-piperidinyl)-piperazine;

(BB) 1-[3,5-dibromo-N-[[4-[1,3-dihydro-4-[3-(trifluoromethyl)phenyl]-2(2H)-oxoimidazol-1-yl]-1-piperidinyl]carbonyl]-D-tyrosyl]-4-(1-piperidinyl)-piperidine;

(BC) 1-[N^6-Acetyl-N^2-[3,5-dibromo-N-[[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-L-lysyl]-4-(4-pyridinyl)-piperazine;

(BD) 1-[3,5-dibromo-N-[[4-(1,3-dihydro-4-phenyl-2(2H)-oxoimidazol-1-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-4-(hexahydro-1H-1-azepinyl)-piperidine;

(BE) 1-[4-amino-3,5-dibromo-N-[[4-(1,3-dihydro-4-(3-thienyl)-2(2H)-oxoimidazol-1-yl)-1-piperidinyl]carbonyl]-D-phenyl-alanyl]-4-(1-methyl-4-piperidinyl)-piperidine;

(BF) 1-[4-amino-3,5-dibromo-N-[[4-[1,3-dihydro-4-[3-(trifluoromethyl)phenyl]-2(2H)-oxoimidazol-1-yl]-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-methyl-4-piperidinyl)-piperidine;

(BG) 1-[3,5-dibromo-N-[[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-4-[1-(hydroxycarbonylmethyl)-4-piperidinyl]-piperidine;

(BH) 1-[4-amino-3,5-dibromo-N-[[4-[3,4-dihydro-2(1H)-oxoquinazolin-3-yl]-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-methylsulphonyl-4-piperidinyl)-piperidine;

(BI) 1-[3,5-dibromo-N-[[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-4-(4-piperidinyl)-piperidine;

(BJ) 1-[4-amino-3,5-dibromo-N-[[4-(1,3-dihydro-4-phenyl-2(2H)-oxoimidazol-1-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-ethyl-4-piperidinyl)-piperidine;

(BK) 1-[4-amino-3,5-dibromo-N-[[4-(1,3-dihydro-4-(3-hydroxyphenyl)-2(2H)-oxoimidazol-1-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-methyl-4-piperidinyl)-piperidine;

(BL) 1-[3,5-dibromo-N-[[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-4-(hexahydro-1H-1-azepinyl)-piperidine;

(BM) 1-[4-amino-3,5-dibromo-N-[[4-(1,3-dihydro-4-phenyl-2(2H)-oxoimidazol-1-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-piperidinyl)-piperidine;

(BN) 1-[4-amino-3,5-dibromo-N-[[4-[4-(3-bromophenyl)-1,3-dihydro-2(2H)-oxoimidazol-1-yl]-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(exo-8-methyl-8-azabicyclo[3,2,1]oct-3-yl)-piperazine;

(BO) 1-[4-amino-3,5-dibromo-N-[[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-ethyl-4-piperidinyl)-piperidine;

(BP) 1-[4-amino-3,5-dibromo-N-[[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-ethyl-4-piperidinyl)-piperazine;

(BQ) 1-[4-amino-3,5-dibromo-N-[[4-[1,3-dihydro-4-(3-methoxyphenyl)-2(2H)-oxoimidazol-1-yl]-1-

piperidinyl]carbonyl]-D-phenylalanyl]-4-(exo-8-methyl-8-azabicyclo[3,2,1]oct-3-yl)-piperazine;

(BR) 1-[3,5-dibromo-N-[[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-4-[1-(cyclopropyl-methyl)-4-piperidinyl]-piperidine;

(BS) 1-[4-amino-3,5-dibromo-N-[[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(hexahydro-1H-1-azepinyl)-piperidine;

(BT) 1-[4-amino-3,5-dibromo-N-[[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(4-piperidinyl)-piperidine;

(BU) 1-[3,5-dibromo-N-[[4-(1,3-dihydro-4-phenyl-2(2H)-oxoimidazol-1-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-4-(4-pyridinyl)-piperidine;

(BV) 1-[3,5-dibromo-N-[[4-[1,3-dihydro-4-[3-(trifluoromethyl)phenyl]-2(2H)-oxoimidazol-1-yl]-1-piperidinyl]carbonyl]-D-tyrosyl]-4-(-methyl-4-piperidinyl)-piperazine;

(BW) 1-[N^2-[3,5-dibromo-N-[[4-[1,3-dihydro-4-[3-(trifluoromethyl)phenyl]-2(2H)-oxoimidazol-1-yl]-1-piperidinyl]carbonyl]-D-tyrosyl]-L-lysyl]-4-(4-pyridinyl)-piperazine;

(BX) 1-[3,5-dibromo-N-[[4-(1,3-dihydro-4-(3-thienyl)-2(2H)-oxoimidazol-1-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-4-(1-piperidinyl)-piperidine;

(BY) 1-[4-amino-N-[[4-[4-(3-chlorophenyl)-1,3-dihydro-2(2H)-oxoimidazol-1-yl]-1-piperidinyl]carbonyl]-3,5-dibromo-D-phenylalanyl]-4-(1-methyl-4-piperidinyl)-piperidine;

(BZ) 1-[4-amino-3,5-dibromo-N-[[4-[1,3-dihydro-4-[3-(trifluoromethyl)phenyl]-2(2H)-oxoimidazol-1-yl]-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(hexahydro-1H-1-azepinyl)-piperidine;

(CA) 1-[4-amino-3,5-dibromo-N-[[4-[1,3-dihydro-4-[3-(trifluoromethyl)phenyl]-2(2H)-oxoimidazol-1-yl]-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-methyl-4-piperidinyl)-piperazine;

(CB) 1-[4-amino-N-[[4-[4-(3-chlorophenyl)-1,3-dihydro-2(2H)-oxoimidazol-1-yl]-1-piperidinyl]carbonyl]-3,5-dibromo-D-phenylalanyl]-4-(hexahydro-1H-1-azepinyl)-piperidine;

(CC) 1-[4-amino-3,5-dibromo-N-[[4-(1,3-dihydro-4-phenyl-2(2H)-oxoimidazol-1-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(4-pyridinyl)-piperazine;

(CD) 1-[3,5-dibromo-N-[[4-(1,3-dihydro-4-phenyl-2(2H)-oxoimidazol-1-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-4-(1-methyl-4-piperidinyl)-piperidine;

(CE) 1-[4-amino-3,5-dibromo-N-[[4-[1,3-dihydro-4-phenyl-2(2H)-oxoimidazol-1-yl]-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-[4-(1-oxoethyl)phenyl]-piperazine;

(CF) 1-[3,5-dibromo-N-[[4-[3,4-dihydro-2(1H)-oxoquinazolin-3-yl]-1-piperidinyl]carbonyl]-D-tyrosyl]-4-(1-methyl-4-piperidinyl)-piperazine;

(CG) 1-[4-amino-3,5-dibromo-N-[[4-[1,3-dihydro-4-(3-nitrophenyl)-2(2H)-oxoimidazol-1-yl]-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(-methyl-4-piperidinyl)-piperidine;

(CH) 1-[4-amino-3,5-dibromo-N-[[4-[3,4-dihydro-2(1H)-oxoquinazolin-3-yl]-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-pyrrolidinyl)-piperidine;

(CI) 1-[4-amino-3,5-dibromo-N-[[4-(1,3-dihydro-4-phenyl-2(2H)-oxoimidazol-1-yl)-1-piperidinyl]

carbonyl]-D-phenylalanyl]-4-(hexahydro-1H-1-azepinyl)-piperidine; and

(CJ) 1-[4-amino-3,5-dibromo-N-[[4-(1,3-dihydro-4-(3-thienyl)-2(2H)-oxoimidazol-1-yl)-1-piperidinyl]carbonyl]-D-phenyl-alanyl]-4-(1-methyl-4-piperidinyl)-piperazine,

the tautomers, the diastereomers, the enantiomers, the mixtures thereof and the physiologically acceptable salts thereof.

6. A pharmaceutical composition for treating menopausal hot flushes comprising an active substance selected from CGRP antagonists and CGRP release inhibitors.

7. The pharmaceutical composition according to claim 6, wherein the pharmaceutical composition contains only one active substance.

8. The pharmaceutical composition according to claim 6, wherein the active substance is a CGRP antagonist.

9. The pharmaceutical composition according to claim 8, wherein the CGRP antagonist is selected from the group consisting of:

(A) 1-[N^2-[3,5-dibromo-N-[[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl) 1-piperidinyl]carbonyl]-D-tyrosyl]-L-lysyl]-4-(4-pyridinyl)-piperazine;

(B) 1-[4-amino-3,5-dibromo-N-[[4-(2,3,4,5-tetrahydro-2(1H)-oxo-1,3-benzodiazepin-3-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-piperidinyl)-piperidine;

(C) 1-[N^2-[4-amino-3,5-dibromo-N-[[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-L-lysyl]-4-(4-pyridinyl)-piperazine;

(D) 1-[N^2-[4-amino-3,5-dibromo-N-[[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-L-lysyl]-4-(4-pyridinyl)-piperidine;

(E) 1-[N^2-[3,5-dibromo-N-[[4-(1,3-dihydro-4-phenyl-2(2H)-oxoimidazol-1-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-L-lysyl]-4-(4-pyridinyl)-piperazine;

(F) 1-[N^2-[4-amino-3,5-dibromo-N-[[4-(1,3-dihydro-4-phenyl-2(2H)-oxoimidazol-1-yl)-1-piperidinyl]carbonyl]-D-phenyl-alanyl]-L-lysyl]-4-(4-pyridinyl)-piperazine;

(G) 1-[3,5-dibromo-N-[[4-(3,4-dihydro-2(1H)-oxothieno[3,4-d]pyrimidin-3-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-4-(1-piperidinyl)-piperidine;

(H) 1-[4-amino-3,5-dibromo-N-[[4-(2,4-dihydro-5-phenyl-3(3H)-oxo-1,2,4-triazol-2-yl)-1-piperidinyl]carbonyl]-D-phenyl-alanyl]-4-(1-methyl-4-piperidinyl)-piperidine;

(I) 1-[4-amino-3,5-dibromo-N-[[4-(2,4-dihydro-5-phenyl-3(3H)-oxo-1,2,4-triazol-2-yl)-1-piperidinyl]carbonyl]-D-phenyl-alanyl]-4-(1-piperidinyl)-piperidine;

(J) 1-[4-amino-3,5-dibromo-N-[[4-(2,4-dihydro-5-phenyl-3(3H)-oxo-1,2,4-triazol-2-yl)-1-piperidinyl]carbonyl]-D-phenyl-alanyl]-4-(1-methyl-4-piperidinyl)-piperazine;

(K) 1-[4-amino-3,5-dibromo-N-[[4-(3,4-dihydro-2(1H)-oxothieno[3,2-d]pyrimidin-3-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-piperidinyl)-piperidine;

(L) 1-[4-amino-3,5-dibromo-N-[[4-[1,3-dihydro-4-[3-(tri-fluoromethyl)phenyl]-2(2H)-oxoimidazol-1-yl]-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-ethyl-4-piperidinyl)-piperidine;

(M) 1-[4-amino-3,5-dibromo-N-[[4-[3,4-dihydro-2(1H)-oxoquinazolin-3-yl]-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-hexyl-4-piperidinyl)-piperidine;

(N) 1-[4-amino-3,5-dibromo-N-[[4-[3,4-dihydro-2(1H)-oxoquinazolin-3-yl]-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-cyclopropylmethyl-4-piperidinyl)-piperidine;

(O) 1-[N-[[4-[3,4-dihydro-2(1H)-oxoquinazolin-3-yl]-1-piperidinyl]carbonyl]-3-ethenyl-D,L-phenylalanyl]-4-(hexahydro-1H-1-azepinyl)-piperidine;

(P) (R,S)-1-[4-[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]-2-[(4-hydroxy-3,5-dimethylphenyl)methyl]-1,4-dioxobutyl]-4-(1-piperidinyl)-piperidine;

(Q) 1-[4-amino-3,5-dibromo-N-[[4-[N-(aminocarbonyl)-N-phenylamino]-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-piperidinyl)-piperidine;

(R) 1-[4-amino-3,5-dibromo-N-[[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(5-methoxy-4-pyrimidinyl)-piperazine;

(S) 1-[4-amino-3,5-dibromo-N-[[4-(1,1-dioxido-3(4H)-oxo-1,2,4-benzothiadiazin-2-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-piperidinyl)-piperidine;

(T) 1-[4-amino-3,5-dibromo-N-[[4-[2(1H)-oxoquinolin-3-yl]-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-piperidinyl)-piperidine;

(U) 1-[4-amino-3,5-dibromo-N-[[4-[3,4-dihydro-2(1H)-oxoquinazolin-3-yl]-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-[3-(dimethylamino)propyl]-piperazine;

(V) 1-[4-amino-3,5-dibromo-N-[[4-[3,4-dihydro-2(1H)-oxoquinazolin-3-yl]-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(4-methyl-1-piperazinyl)-piperidine;

(W) 1-[4-amino-3,5-dibromo-N-[[4-[3,4-dihydro-2(1H)-oxoquinazolin-3-yl]-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-[(1-methyl-4-piperidinyl)carbonyl]-piperazine;

(X) 1-[4-amino-3,5-dibromo-N-[[4-[3,4-dihydro-2(1H)-oxoquinazolin-3-yl]-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-[(1-methyl-4-piperazinyl)carbonyl]-piperazine;

(Y) 1-[4-amino-3,5-dibromo-N-[[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-[4-[4-(dimethylamino)butyl]phenyl]-piperazine;

(Z) 1-[4-amino-3,5-dibromo-N-[[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-[4-(dimethylamino)-1-piperidinyl]-piperidine;

(AA) 1-[N^2-[[4-(1,3-dihydro-4-phenyl-2(2H)-oxoimidazol-1-yl)-1-piperidinyl]carbonyl]-N'-methyl-D-tryptyl]-4-(4-methyl-1-piperazinyl)-piperidine;

(AB) 1-[N^2-[[4-(1,3-dihydro-4-phenyl-2(2H)-oxoimidazol-1-yl)-1-piperidinyl]carbonyl]-N'-(1,1-dimethylethoxycarbonyl)-D-tryptyl]-4-(1-methyl-4-piperidinyl)-piperidine;

(AC) (R,S)-1-[4-[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]-2-[(3,5-dibromo-4-methylphenyl)methyl]-1,4-dioxobutyl]-4-(4-methyl-1-piperazinyl)-piperidine;

(AD) (R,S)-1-[4-[1-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]-2-[(3,5-dibromo-4-methoxyphenyl)methyl]-1,4-dioxobutyl]-4-(-methyl-4-piperidinyl)-piperidine;

(AE) (R,S)-1-[4-[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]-2-[(3,4-dibromophenyl)methyl]-1,4-dioxobutyl]-4-(4-methyl-1-piperazinyl)-piperidine;

(AF) 1-[N^2-[N-[[4-(1,3-dihydro-2(2H)-oxobenzimidazol-1-yl)-1-piperidinyl]carbonyl]-3,5-dibromo-D-tyrosyl]-L-lysyl]-4-(4-pyridinyl)-piperazine;

(AG) 1-[4-amino-3,5-dibromo-N-[[4-(1,3-dihydro-6-hydroxy-2(2H)-oxobenzimidazol-1-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-piperidinyl)-piperidine;

(AH) 1-[N^2-[4-amino-3,5-dibromo-N-[[4-(1,3-dihydro-2(2H)-oxobenzimidazol-1-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-N^6,N^6-dimethyl-L-lysyl]-4-(4-pyridinyl)-piperazine;

(AI) 1-[N^2-[4-amino-3,5-dibromo-N-[[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-N^6,N^6-dimethyl-L-lysyl]-4-(4-pyridinyl)-piperazine;

(AJ) (R,S)-1-[2-(4-amino-3,5-dibromobenzoyl)-4-[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]-4-oxobutyl]-4-(1-piperidinyl)-piperidine;

(AK) 1-[4-amino-3,5-dibromo-N-[[4-(3,4-dihydro-2,2-dioxido-2,1,3-benzothiadiazin-3-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-piperidinyl)-piperidine;

(AL) 1-[4-amino-3,5-dibromo-N-[[4-[1,3-dihydro-2(2H)-oxoimidazo[4,5-c]quinolin-3yl]-1-piperidinyl]carbonyl]-D-phenyl-alanyl]-4-(1-piperidinyl)carbonyl]-piperidine;

(AM) 1-[4-amino-3,5-dibromo-N-[[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-piperidinyl)-piperidine;

(AN) 1-[N^2-[3,5-dibromo-N-[[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-N^6,N^6-dimethyl-L-lysyl]-4-(4-pyridinyl)-piperazine;

(AO) 1-[4-amino-N-[[4-[4-(3-bromophenyl)-1,3-dihydro-2(2H)-oxoimidazol-1-yl]-1-piperidinyl]carbonyl]-3,5-dibromo-D-phenylalanyl]-4-(1-methyl-4-piperidinyl)-piperidine;

(AP) 1-[4-amino-3,5-dibromo-N-[[4-[1,3-dihydro-4-phenyl-2(2H)-oxoimidazol-1-yl]-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(4-methyl-1-piperazinyl)-piperidine;

(AQ) 1-[4-amino-3,5-dibromo-N-[[4-[1,3-dihydro-4-[3-(trifluoromethyl)phenyl]-2(2H)-oxoimidazol-1-yl]-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-piperidinyl)-piperidine;

(AR) 1-[4-amino-3,5-dibromo-N-[[4-[1,3-dihydro-4-[3-(trifluoromethyl)phenyl]-2(2H)-oxoimidazol-1-yl]-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(exo-8-methyl-8-azabicyclo[3,2,1]oct-3-yl)-piperazine;

(AS) 1-[3,5-dibromo-N-[[4-(1,3-dihydro-4-phenyl-2(2H)-oxoimidazol-1-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-4-(1-piperidinyl)-piperidine;

(AT) 1-[4-amino-3,5-dibromo-N-[[4-[1,3-dihydro-4-[3-(trifluoromethyl)phenyl]-2(2H)-oxoimidazol-1-yl]-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-ethyl-4-piperidinyl)-piperazine;

(AU) 1-[4-amino-3,5-dibromo-N-[[4-[1,3-dihydro-4-phenyl-2(2H)-oxoimidazol-1-yl]-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(hexahydro-4-methyl-1H-1,4-diazepin-1-yl)piperidine;

(AV) 1-[3,5-dibromo-N-[[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-4-[1-(methylsulfonyl)-4-piperidinyl]-piperidine;

(AW) 1-[4-amino-3,5-dibromo-N-[[4-(1,3-dihydro-4-phenyl-2(2H)-oxoimidazol-1-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-methyl-4-piperidinyl)-piperidine;

(AX) 1-[3,5-dibromo-N-[[4-[1,3-dihydro-4-[3-(trifluoromethyl)phenyl]-2(2H)-oxoimidazol-1-yl]-1-piperidinyl]carbonyl]-D-tyrosyl]-4-(hexahydro-1H-1-azepinyl)-piperidine;

(AY) 1-[3,5-dibromo-N-[[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-4-(1-methyl-4-piperidinyl)-piperidine;

(AZ) 1-[4-amino-3,5-dibromo-N-[[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(exo-8-methyl-8-azabicyclo[3,2,1]oct-3-yl)-piperazine;

(BA) 1-[4-amino-3,5-dibromo-N-[[4-(1,3-dihydro-4-phenyl-2(2H)-oxoimidazol-1-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-methyl-4-piperidinyl)-piperazine;

(BB) 1-[3,5-dibromo-N-[[4-[1,3-dihydro-4-[3-(trifluoromethyl)phenyl]-2(2H)-oxoimidazol-1-yl]-1-piperidinyl]carbonyl]-D-tyrosyl]-4-(1-piperidinyl)-piperidine;

(BC) 1-[N^6-Acetyl-N^2-[3,5-dibromo-N-[[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-L-lysyl]-4-(4-pyridinyl)-piperazine;

(BD) 1-[3,5-dibromo-N-[[4-(1,3-dihydro-4-phenyl-2(2H)-oxoimidazol-1-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-4-(hexahydro-1H-1-azepinyl)-piperidine;

(BE) 1-[4-amino-3,5-dibromo-N-[[4-(1,3-dihydro-4-(3-thienyl)-2(2H)-oxoimidazol-1-yl)-1-piperidinyl]carbonyl]-D-phenyl-alanyl]-4-(1-methyl-4-piperidinyl)-piperidine;

(BF) 1-[4-amino-3,5-dibromo-N-[[4-[1,3-dihydro-4-[3-(trifluoromethyl)phenyl]-2(2H)-oxoimidazol-1-yl]-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-methyl-4-piperidinyl)-piperidine;

(BG) 1-[3,5-dibromo-N-[[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-4-[1-(hydroxycarbonylmethyl)-4-piperidinyl]-piperidine;

(BH) 1-[4-amino-3,5-dibromo-N-[[4-[3,4-dihydro-2(1H)-oxoquinazolin-3-yl]-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-methylsulphonyl-4-piperidinyl)-piperidine;

(BI) 1-[3,5-dibromo-N-[[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-4-(4-piperidinyl)-piperidine;

(BJ) 1-[4-amino-3,5-dibromo-N-[[4-(1,3-dihydro-4-phenyl-2(2H)-oxoimidazol-1-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-ethyl-4-piperidinyl)-piperidine;

(BK) 1-[4-amino-3,5-dibromo-N-[[4-(1,3-dihydro-4-(3-hydroxyphenyl)-2(2H)-oxoimidazol-1-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-methyl-4-piperidinyl)-piperidine;

(BL) 1-[3,5-dibromo-N-[[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-4-(hexahydro-1H-1-azepinyl)-piperidine;

(BM) 1-[4-amino-3,5-dibromo-N-[[4-(1,3-dihydro-4-phenyl-2(2H)-oxoimidazol-1-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-piperidinyl)-piperidine;

(BN) 1-[4-amino-3,5-dibromo-N-[[4-[4-(3-bromophenyl)-1,3-dihydro-2(2H)-oxoimidazol-1-yl]-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(exo-8-methyl-8-azabicyclo[3,2,1]oct-3-yl)-piperazine;

(BO) 1-[4-amino-3,5-dibromo-N-[[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-ethyl-4-piperidinyl)-piperidine;

(BP) 1-[4-amino-3,5-dibromo-N-[[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-ethyl-4-piperidinyl)-piperazine;

(BQ) 1-[4-amino-3,5-dibromo-N-[[4-[1,3-dihydro-4-(3-methoxyphenyl)-2(2H)-oxoimidazol-1-yl]-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(exo-8-methyl-8-azabicyclo[3,2,1]oct-3-yl)-piperazine;

(BR) 1-[3,5-dibromo-N-[[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-4-[1-(cyclopropyl-methyl)-4-piperidinyl]-piperidine;

(BS) 1-[4-amino-3,5-dibromo-N-[[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(hexahydro-1H-1-azepinyl)-piperidine;

(BT) 1-[4-amino-3,5-dibromo-N-[[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(4-piperidinyl)-piperidine;

(BU) 1-[3,5-dibromo-N-[[4-(1,3-dihydro-4-phenyl-2(2H)-oxoimidazol-1-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-4-(4-pyridinyl)-piperidine;

(BV) 1-[3,5-dibromo-N-[[4-[1,3-dihydro-4-[3-(trifluoromethyl)phenyl]-2(2H)-oxoimidazol-1-yl]-1-piperidinyl]carbonyl]-D-tyrosyl]-4-(1-methyl-4-piperidinyl)-piperazine;

(BW) 1-[N^2-[3,5-dibromo-N-[[4-[1,3-dihydro-4-[3-(trifluoromethyl)phenyl]-2(2H)-oxoimidazol-1-yl]-1-piperidinyl]carbonyl]-D-tyrosyl]-L-lysyl]-4-(4-pyridinyl)-piperazine;

(BX) 1-[3,5-dibromo-N-[[4-(1,3-dihydro-4-(3-thienyl)-2(2H)-oxoimidazol-1-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-4-(1-piperidinyl)-piperidine;

(BY) 1-[4-amino-N-[[4-[4-(3-chlorophenyl)-1,3-dihydro-2(2H)-oxoimidazol-1-yl]-1-piperidinyl]carbonyl]-3,5-dibromo-D-phenylalanyl]-4-(1-methyl-4-piperidinyl)-piperidine;

(BZ) 1-[4-amino-3,5-dibromo-N-[[4-[1,3-dihydro-4-[3-(trifluoromethyl)phenyl]-2(2H)-oxoimidazol-1-yl]-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(hexahydro-1H-1-azepinyl)-piperidine;

(CA) 1-[4-amino-3,5-dibromo-N-[[4-[1,3-dihydro-4-[3-(trifluoromethyl)phenyl]-2(2H)-oxoimidazol-1-yl]-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-methyl-4-piperidinyl)-piperazine;

(CB) 1-[4-amino-N-[[4-[4-(3-chlorophenyl)-1,3-dihydro-2(2h)-oxoimidazol-1-yl]-1-piperidinyl]carbonyl]-3,5-dibromo-D-phenylalanyl]-4-(hexahydro-1H-1-azepinyl)-piperidine;

(CC) 1-[4-amino-3,5-dibromo-N-[[4-(1,3-dihydro-4-phenyl-2(2H)-oxoimidazol-1-yl)-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(4-pyridinyl)-piperazine;

(CD) 1-[3,5-dibromo-N-[[4-(1,3-dihydro-4-phenyl-2(2H)-oxoimidazol-1-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-4-(1-methyl-4-piperidinyl)-piperidine;

(CE) 1-[4-amino-3,5-dibromo-N-[[4-[1,3-dihydro-4-phenyl-2(2H)-oxoimidazol-1-yl]-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-[4-(1-oxoethyl)phenyl]-piperazine;

(CF) 1-[3,5-dibromo-N-[[4-[3,4-dihydro-2(1H)-oxoquinazolin-3-yl]-1-piperidinyl]carbonyl]-D-tyrosyl]-4-(1-methyl-4-piperidinyl)-piperazine;

(CG) 1-[4-amino-3,5-dibromo-N-[[4-[1,3-dihydro-4-(3-nitrophenyl)-2(2H)-oxoimidazol-1-yl]-1-piperidinyl] carbonyl]-D-phenylalanyl]-4-(1-methyl-4-piperidinyl)-piperidine;

(CH) 1-[4-amino-3,5-dibromo-N-[[4-[3,4-dihydro-2(1H)-oxoquinazolin-3-yl]-1-piperidinyl]carbonyl]-D-phenylalanyl]-4-(1-pyrrolidinyl)-piperidine;

(CI) 1-[4-amino-3,5-dibromo-N-[[4-(1,3-dihydro-4-phenyl-2(2H)-oxoimidazol-1-yl)-1-piperidinyl] carbonyl]-D-phenylalanyl]-4-(hexahydro-1H-1-azepinyl)-piperidine; and

(CJ) 1-[4-amino-3,5-dibromo-N-[[4-(1,3-dihydro-4-(3-thienyl)-2(2H)-oxoimidazo]-1-yl)-1-piperidinyl] carbonyl]-D-phenyl-alanyl]-4-(1-methyl-4-piperidinyl)-piperazine,

the tautomers, the diastereomers, the enantiomers, the mixtures thereof and the physiologically acceptable salts thereof.

10. The pharmaceutical composition according to claim **6**, further comprising one or more inert carriers and/or diluents.

11. The pharmaceutical composition according to claim **7**, further comprising one or more inert carriers and/or diluents.

12. The pharmaceutical composition according to claim **8**, further comprising one or more inert carriers and/or diluents.

13. The pharmaceutical composition according to claim **9**, further comprising one or more inert carriers and/or diluents.

* * * * *

EXHIBIT G

29th EDITION

DORLAND'S Illustrated MEDICAL DICTIONARY

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va·sal·gia (və-sal'jə) angialgia.

va·sa·li·um (və-sa'lē-əm) true vascular tissue, such as is found in closed or vascular organs.

Vas·co·ray (vas'ko-ra) trademark for a preparation of iothalamate meglumine and iothalamate sodium.

vas·cu·lar (vas'ku-lər) 1. pertaining to vessels, particularly blood vessels; called also *vasal*. 2. having a copious blood supply.

vas·cu·lar·i·ty (vas"ku-lar'ĭ-te) the condition of being vascular.

vas·cu·lar·iza·tion (vas"ku-lər-ĭ-za'shən) 1. the process of becoming vascular. 2. angiogenesis. 3. the surgically induced development of vessels in a tissue.

vas·cu·lar·ize (vas'ku-lər-īz) to supply with vessels.

vas·cu·la·ture (vas'ku-lə-chər) 1. circulatory system. 2. any specific part of the circulatory system.

vas·cu·lit·ic (vas"ku-lit'ik) pertaining to vasculitis.

vas·cu·li·tis (vas"ku-li'tis) [*vasculum* + *-itis*] [MeSH: Vasculitis] inflammation of a blood or lymph vessel; see *arteritis, lymphangitis,* and *phlebitis.* Called also *angiitis.*
allergic v., hypersensitivity v.
Churg-Strauss v., see under *syndrome.*
consecutive v., vasculitis caused by extension of the inflammation from the neighboring tissues.
granulomatous v. of central nervous system, granulomatous cerebral v., isolated v. of central nervous system.
hypersensitivity v., a group of systemic necrotizing vasculitides thought to represent hypersensitivity to an antigenic stimulus, such as a drug, infectious agent, or exogenous or endogenous protein; all disorders in this group involve the small vessels. Types include varieties of Schönlein-Henoch purpura and serum sickness, as well as urticarial v. Called also *allergic* or *leukocytoclastic v.* and *hypersensitivity* or *leukocytoclastic angiitis.*
hypocomplementemic v., hypersensitivity vasculitis accompanied by hypocomplementemia.
isolated v. of central nervous system, an idiopathic vasculitis affecting small and medium-sized intracranial vessels, marked by headache, progressive intellectual deterioration, and recurrent cerebral infarcts; some show segmental markings of small arteries on an angiogram, and some have evidence of pleocytosis and elevated protein in the cerebrospinal fluid. Called also *granulomatous v. of central nervous system, granulomatous cerebral v.*, and *isolated angiitis of central nervous system.*
leukocytoclastic v., hypersensitivity v.
livedo v., segmented hyalinizing v.
necrotizing v., see *systemic necrotizing v.*
nodular v., a chronic vasculitis of the lower legs, usually seen in young or middle-aged women, with an unknown etiology; characteristics include painful, reddish blue nodular lesions that may ulcerate, leaving scars, or resorb, leaving atrophic depressions. In the late stages, the subcutaneous fat is replaced by fibrosis and atrophy. See also *erythema induratum.*
overlap v., polyangiitis overlap syndrome.
pulmonary v., any of numerous inflammatory conditions of the walls of the pulmonary vessels; the most common ones are allergic granulomatous angiitis and Wegener's granulomatosis.
rheumatoid v., systemic vasculitis associated with rheumatoid arthritis, affecting small and medium-sized vessels, and generally occurring in patients with long-standing disease, rheumatoid nodules, and a high titer of rheumatoid factor.
segmented hyalinizing v., a chronic relapsing vasculitis of the lower legs, usually affecting middle-aged persons; lesions are nodular or purpuric at the onset and later become superficially ulcerated, resulting in scars; histologically, endothelial proliferations, hyaline degeneration, and thrombosis are seen in the mid and lower dermis. Called also *livedo v.*
systemic v., systemic necrotizing v., any of a group of disorders characterized by inflammation and necrosis of blood vessels, occurring in a broad spectrum of cutaneous and systemic disorders. It includes Churg-Strauss syndrome, polyarteritis nodosa, polyangiitis overlap syndrome, the various kinds of hypersensitivity vasculitis, and other conditions. Called also *necrotizing v.* or *angiitis.*
urticarial v., a type of hypersensitivity vasculitis in which urticaria lasts more than 24 hours, often with systemic symptoms such as arthralgias, arthritis, nephritis, and abdominal pain; many patients also have hypocomplementemia *(hypocomplementemic vasculitis).* The condition may be idiopathic or secondary to a disorder such as systemic lupus erythematosus or Sjögren's syndrome.

vas·cu·lo·gen·e·sis (vas"ku-lo-jen'ə-sis) [*vasculum* + *-genesis*] angiogenesis.

vas·cu·lo·gen·ic (vas"ku-lo-jen'ik) angiogenic (def. 1).

vas·cu·lo·lym·phat·ic (vas"ku-lo-lim-fat'ik) pertaining to blood or lymph vessels.

vas·cu·lo·mo·tor (vas"ku-lo-mo'tor) vasomotor.

vas·cu·lop·a·thy (vas"ku-lop'ə-the) any disorder of blood vessels.

vas·cu·lo·tox·ic (vas"ku-lo-tok'sik) pertaining to or characterized by a deleterious or toxic effect on the vessels of the body.

vas·cu·lum (vas'ku-ləm) [L., dim. of *vas*] a small vessel.
v. aber'rans, vas aberrans.

va·sec·to·mized (və-sek'tə-mīzd) having undergone removal of the ductus deferentes (vasa deferentia) by surgical means.

va·sec·to·my (və-sek'tə-me) [*vas* + *-ectomy*] [MeSH: Vasectomy] surgical removal of the ductus (vas) deferens, or of a portion of it; done to induce infertility or in association with prostatectomy. Called also *vasoresection* and *vasosection.*
cross-over v., vasectomy in which the right and the left vas deferens are transected, the lower portion of each (the portions still attached to the epididymis) then being tied together. The technique prevents recanalization while allowing surgical reconstruction.

Va·se·ret·ic (vas-ə-ret'ik) trademark for a preparation of enalapril maleate and hydrochlorothiazide.

vas·i·fac·tive (vas"ĭ-fak'tiv) [*vas* + L. *facere* to make] angiogenic (def. 1).

vas·i·form (vas'ĭ-form) [*vas* + *form*] having the appearance of a vessel.

va·si·tis (və-si'tis) deferentitis.

vas(o)- [L. *vas*, q.v.] a combining form denoting relationship to a vessel or to a duct.

vaso-ac·tive (vas"o-, va"zo-ak'tiv) said of a chemical that exerts an effect upon the caliber of blood vessels.

vaso-con·stric·tion (vas"o-, va"zo-kən-strik'shən) [MeSH: Vasoconstriction] the diminution of the caliber of vessels, especially constriction of arterioles leading to decreased blood flow to a part.

vaso-con·stric·tive (vas"o-, va"zo-kən-strik'tiv) pertaining to, characterized by, or producing vasoconstriction.

vaso-con·stric·tor (vas"o-, va"zo-kən-strik'tər) 1. causing constriction of the blood vessels. 2. a motor nerve or chemical compound that causes constriction of the blood vessels.

vaso-de·pres·sion (vas"o, va"zo-de-presh'ən) decrease in vascular resistance with hypotension.

vaso-de·pres·sor (vas"o-, va"zo-de-pres'ər) 1. having the effect of lowering the blood pressure through reduction in peripheral resistance. 2. an agent that causes vasodepression.

Va·so·di·lan (va"zo-dī'lan) trademark for preparations of isoxsuprine hydrochloride.

vaso-di·la·ta·tion (vas"o-, va"zo-dī-lə-ta'shən) vasodilation.

vaso-di·la·tion (vas"o-, va"zo-dī-la'shən) [MeSH: Vasodilation] dilation of a vessel, especially dilation of arterioles leading to increased blood flow to a part; extreme, abnormal vasodilation is called *angiectasis.* Called also *vasodilatation.*
reflex v., vasodilation occurring as a reflex response to stimuli applied elsewhere, or subsequent to an initial vasoconstrictive response.

vaso-di·la·tive (vas"o-, va"zo-dī-la'tiv) pertaining to, characterized by, or producing vasodilatation.

vaso-di·la·tor (vas"o-, va"zo-dī'la-tər) 1. causing dilation of the blood vessels. 2. a motor nerve or chemical compound that causes dilation of the blood vessels.

vaso-epi-did·y·mog·ra·phy (vas"o-, va"zo-ep"ĭ-did"ĭ-mog'rə-fe) radiography of the vas deferens and epididymis after injection of a contrast medium.

vaso-epi-did·y·mos·to·my (vas"o-, va"zo-ep"ĭ-did-ĭ-mos'tə-me) operative formation of a communication between the ductus (vas) deferens and the epididymis.

vaso-fac·tive (vas"o-, va"zo-fak'tiv) angiogenic (def. 1).

vaso-for·ma·tive (vas"o-, va"zo-for'mə-tiv) angiogenic (def. 1).

vaso-gan·gli·on (vas"o-, va"zo-gang'gle-on) any vascular ganglion or rete.

va·sog·ra·phy (va-zog'rə-fe) [*vaso-* + *-graphy*] angiography.

vaso-hy·per·ton·ic (vas"o-, va"zo-hī"pər-ton'ik) vasoconstrictor (def. 1).

vaso-hy·po·ton·ic (vas"o-, va"zo-hī"po-ton'ik) vasodilator (def. 1).

vaso-in·ert (vas"o-, va"zo-in-ərt') exerting no effect on the caliber of blood vessels.

vaso-in·hib·i·tor (vas"o-, va"zo-in-hib'ĭ-tər) an agent that inhibits the action of the vasomotor nerves.

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